Title: A Phase 1b, Dose Escalation Study to Determine the Recommended Phase 2 Dose of TAK-659 in Combination With Bendamustine (±Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib for the Treatment of Patients With Advanced Non-Hodgkin Lymphoma After At Least 1 Prior Line of Therapy

NCT Number: NCT02954406

Protocol Approve Date: 15 November 2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase 1b, Dose Escalation Study to Determine the Recommended Phase 2 Dose of TAK-659 in Combination With Bendamustine (±Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib for the Treatment of Patients With Advanced Non-Hodgkin Lymphoma After At Least 1 Prior Line of Therapy

A Phase 1b, Dose Escalation of TAK-659 in Combination With Bendamustine (±Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib in Patients With Advanced Non-Hodgkin Lymphoma

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

40 Landsdowne Street, Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "sponsor", or "Takeda"

Study Number: C34005

IND Number: 119,231 **EudraCT Number:** 2016-001426-34

Compound: TAK-659

Date: 15 November 2018 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
07 June 2016	Initial Protocol	Not applicable	Global
08 February 2017	01	Not applicable	Global
22 May 2018	02	Not applicable	Not applicable [a]
15 November 2018	03	Not applicable	Global

[a] Protocol Amendment 02 was not activated.

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1.0 ADMINISTRATIVE INFORMATION

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.

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.

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

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1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (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

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INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 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 or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the Protocol Incorporating Amendment 03. As Protocol Amendment 02 was not activated, the changes described below are based on a comparison with Amendment 01. The overall rationale for Amendment 03 is to close enrollment to Cohorts A, C, D, and E and to restrict the study population in the Cohort B expansion phase to patients with advanced follicular lymphoma (FL) or marginal zone lymphoma (MZL).

A summary of major revisions is 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 I.

Changes in Amendment 03 (Compared With Amendment 01)

1. Added Investigational New Drug (IND) number and EudraCT number to title page.
2. Revised background to include information on FL, update description of TAK-659, reorganize nonclinical pharmacology information for TAK-659 combination therapy, and update clinical data for TAK-659.
3. Reorganized and updated potential benefits and risks of TAK-659.
4. Reorganized and updated study rationale.
5. Revised study design to restrict the expansion phase of the study to Cohort B only, and added text to permit evaluation of intermittent once-daily (QD) dosing schedules in Cohort B if appropriate.
6. Restricted study population in Cohort B expansion phase to patients with advanced FL or MZL.
7. Revised study sample size determination and planned enrollment numbers for each cohort.
8. Revised planned dose levels of TAK-659.
9. Revised duration of an individual patient's study participation.
10. Extended total study duration.
11. Specified number of prior lines of therapy for patients entering Cohort B expansion phase and clarified the definition of lines of therapy.
12. Revised method for measuring renal function.
13. Added requirement for controlled fasting serum glucose levels during screening.
14. Added requirement that women of childbearing potential must have a negative serum pregnancy test at screening.

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15. Added requirement that female patients should not donate ova from time of signing informed consent through 180 days after last dose of study drug.
16. Added requirement that male patients should not donate sperm from time of signing informed consent through 180 days after last dose of study drug.
17. Clarified exclusion criteria related to prior anticancer treatment and prior autologous stem cell transplant.
18. Clarified exclusion criterion related to cardiovascular conditions.
19. Updated definitions of dose-limiting toxicity.
20. Revised dose modification guidelines for hematologic and nonhematologic toxicities.
21. Revised retreatment criteria for Cohorts A, B, and C.
22. Reorganized and updated management of TAK-659–related clinical events.
23. Added a section heading for management of combination drug-related clinical events.
24. Added sparse PK sampling schedule for Cohort B expansion phase, and clarified PK and PD sampling schedules for Cohort B when intermittent QD dosing schedule is used.
25. Added progression-free survival (PFS) follow-up visits for patients in Cohort B expansion phase who discontinue treatment for any reason other than progressive disease.
26. Updated procedures for cytomegalovirus monitoring.
27. Removed residual bone marrow sample collections from study procedures.
28. CCI [redacted]
29. CCI [redacted]
30. Revised reasons for discontinuation of treatment with study drug.
31. Revised reasons for withdrawal of patients from study.
32. Added criteria for early discontinuation of study.
33. Added PFS as a secondary endpoint for patients in Cohort B expansion phase.
34. Added a urine pregnancy test for women of childbearing potential at end of treatment for each cohort.
35. Added vital sign measurements on Day 15 of Cycle 3 and beyond for Cohorts A, B, and C.
36. Updated reference citations to support background information in protocol and added reference citation for a published TAK-659 clinical study.
37. Added a recommendation that prophylaxis for varicella-zoster virus should be administered for all patients in Cohort B.
38. Added a recommendation that the prophylaxis for *Pneumocystis jiroveci* pneumonia should be administered for all patients in Cohort B.

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc.		**Compound:** TAK-659
Title of Protocol: A Phase 1b, Dose Escalation Study to Determine the Recommended Phase 2 Dose of TAK-659 in Combination With Bendamustine (± Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib for the Treatment of Patients With Advanced Non-Hodgkin Lymphoma After At Least 1 Prior Line of Therapy	**IND No.:** 119,231	**EudraCT No.:** 2016-001426-34
Study Number: C34005		**Phase:** 1b

Study Design:

This is a phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination drugs (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, or ibrutinib) in adult patients with advanced non-Hodgkin lymphoma (NHL) after at least 1 prior line of therapy. The primary objective of the study is to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) of TAK-659 when administered with each of the combination drugs.

Once enrolled in the study, patients will be assigned to 1 of 5 combination cohorts:

- Cohort A (TAK-659 + bendamustine).
- Cohort B (TAK-659 + bendamustine + rituximab).
- Cohort C (TAK-659 + gemcitabine).
- Cohort D (TAK-659 + lenalidomide).
- Cohort E (TAK-659 + ibrutinib).

This study comprises 2 phases: a dose escalation phase and a safety expansion phase. Patients in all 5 cohorts (Cohorts A-E) will participate in the dose escalation phase of the study.

During the dose escalation phase, the dose of TAK-659 will be escalated (3 planned dose levels of escalation: 60, 80, and 100 mg) according to a 3 + 3 dose escalation scheme. The dose of oral TAK-659 will increase in 20-mg increments to a maximum of 100 mg once daily (QD), provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose levels below the starting dose of 60 mg QD (eg, 40 mg QD) or intermittent QD dosing schedules (eg, 7 days on followed by 7 days off or 14 days on followed by 7 days off) also may be evaluated, if appropriate, in Cohort B. Dose escalation will continue until the MTD is reached, or until TAK-659 100 mg QD (the maximally administered dose [MAD]) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified based on the safety, tolerability, and preliminary pharmacokinetic (PK) and efficacy data (if available) observed in Cycle 1 and beyond.

The doses of combination drugs will be administered at a fixed dose and regimen.

During the safety expansion phase of the study, approximately 12 additional patients with advanced follicular lymphoma (FL) or marginal zone lymphoma (MZL) will be added to Cohort B at the MTD/MAD/RP2D for further safety evaluation. No patients from Cohorts A, C, D, or E will enter the safety expansion phase of the study because effective 16 March 2018, the sponsor closed recruitment into Cohorts C, D, and E and effective 16 October 2018, the sponsor closed recruitment into Cohort A.

During both the dose escalation phase and the safety expansion phase of the study, PK samples will be collected at prespecified time points to characterize the PK of TAK-659 when administered with each of the combination drugs. Pharmacodynamic and other biomarker analyses will also be performed for TAK-659 in combination with each of the combination drugs. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [1].

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Primary Objective: To determine the MTD or RP2D for TAK-659 when administered in combination with each of the combination drugs (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib).

Secondary Objectives:

- To characterize the plasma PK of TAK-659 in each of the 5 cohorts.
- To observe the preliminary efficacy of different combination drugs with TAK-659 (Cohorts A-E) in patients with advanced NHL who have relapsed and/or are refractory after ≥1 prior line of therapy (for patients with FL or MZL in Cohort B expansion, ≤1 prior line of therapy).

Additional Objective: To evaluate the safety and tolerability of TAK-659 in each of the 5 cohorts.

Exploratory Objectives:

CCI [redacted]

Patient Population: Patients with advanced NHL of any histology after at least 1 prior line of therapy.

Number of Patients:

Patients will be enrolled and assigned to 1 of 5 combination cohorts as follows:

Cohort	Total (~N) [a]	Dose Escalation (~N)	Safety Expansion (~N)
A	14	9-12	0 [b]
B	40	9-24 [c]	12
C	14	9-12	0 [b]
D	14	9-12	0 [b]
E	14	9-12	0 [b]

[a] Approximate enrolled number was based on the assumption of a 10% dropout rate.
[b] Effective 16 March 2018, enrollment into Cohorts C, D, and E was closed, and effective 16 October 2018, enrollment into Cohort A was closed. No patients from these 4 cohorts will enter into the safety expansion phase of this study.
[c] A dose lower than 60 mg QD or intermittent dosing schedules may be evaluated, if appropriate.

Number of Sites:

Estimated total: ~15 sites in North America and Europe.

Dose Levels and Routes of Administration:

TAK-659 Dosage Regimen: Oral TAK-659 will start at a dose of 60 mg QD and may be increased in 20-mg increments to 100 mg QD in combination with each of the following combination drugs:

Cohort	Study Drug(s)	Dosage Regimen(s) of Combination Drug(s)
A	TAK-659 + 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	TAK-659 + 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 administered IV per local guidelines and labeling on Day 1 of

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		each 21-day cycle, up to 8 cycles
C	TAK-659 + gemcitabine	1000 mg/m^2 IV infusion over 30 min on Days 1 and 8 of each 21-day cycle
D	TAK-659 + lenalidomide	25 mg orally (PO) QD for Days 1-21 of each 28-day cycle
E	TAK-659 + ibrutinib	560 mg PO QD of each 28-day cycle

Duration of Treatment:	**Period of Evaluation:**
Treatment will continue until disease progression, unacceptable toxicities, or withdrawal due to other reasons. Estimated treatment duration is 12 months.	Patients will be followed for safety for 28 days after the last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first.

Main Criteria for Inclusion:

- Male or female patients aged 18 years or older.
- In the dose escalation phase, histologically or cytologically confirmed diagnosis of advanced NHL of any histology (with the exception of patients with Waldenström macroglobulinemia and chronic lymphocytic leukemia). In the safety expansion phase for Cohort B, only patients with advanced FL or MZL will be included.
- Radiographically or clinically measurable disease with at least 1 target lesion per International Working Group criteria (IWG) for malignant lymphoma [2].
- In the dose escalation phase, patients who are refractory or relapsed after at least 1 prior line of therapy due to progression, intolerance, or physician/patient decision and for whom no effective standard therapy is available per the investigator's assessment. In the safety expansion phase for Cohort B in patients with FL or MZL, the prior line of therapy is limited to ≤1.
- Eastern Cooperative Oncology Group performance status score of 0 or 1 and life expectancy of greater than 3 months.
- Patients must have adequate organ function, including the following:
  - Adequate bone marrow reserve: absolute neutrophil count ≥1000/μL, platelet count ≥75,000/μL (≥50,000/μL for patients with bone marrow involvement), and hemoglobin ≥8 g/dL (red blood cell and platelet transfusion allowed ≥14 days before assessment).
  - Hepatic: total bilirubin ≤1.5 times the upper limit of the normal range (ULN); alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN.
  - Renal: creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault equation.
  - 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 antihypertensive medications).
    - Fasting serum glucose level shall be controlled to 130 mg/dL during screening period.
- Both men and women in Cohort D (TAK-659 + lenalidomide) must adhere to the guidelines of the RevAssist program (United States participants) or the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the study manual (all other participants who are not using commercial supplies).

Main Criteria for Exclusion:

In addition to the standard exclusion criteria:

- Central nervous system lymphoma; active brain or leptomeningeal metastases, as indicated by positive cytology from lumbar puncture or computed tomography scan/magnetic resonance imaging. Exceptions include those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least

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2 weeks after completion of the definitive therapy and steroids, and do not have neurologic dysfunction that would confound the evaluation of neurologic and other adverse events (AEs).

- Known human immunodeficiency virus (HIV)-related malignancy.
- Known HIV positive.
- Systemic anticancer treatment (including investigational agents) or radiotherapy less than 2 weeks before the first dose of study treatment (≤4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine).
- Prior autologous stem cell transplant (ASCT) within 6 months or prior ASCT at any time without adequate hematopoietic recovery, defined by the entry criteria in the study, before Cycle 1 Day 1, or allogeneic stem cell transplant any time.
- 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 in cases in which an AE must be managed (see Section 8.5).
  - 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 in cases in which an AE must be managed (see Section 8.5).
  - 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.
- Additionally, for patients in Cohort E (TAK-659 + ibrutinib), use or consumption of any of the following substances:
  - Medications or supplements that are known to be moderate 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 drugs. In general, the use of these agents is not permitted during the study for this combination except in cases in which an AE must be managed (see Section 8.5).
  - Medications or supplements that are known to be moderate mechanism-based inhibitors or moderate inducers of CYP3A within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drugs. In general, the use of these agents is not permitted during the study for this combination except in cases in which an AE must be managed (see Section 8.5).
  - Seville oranges within 5 days before the first dose of study drugs and during the study.

Main Criteria for Evaluation and Analyses:

- Primary Endpoints:
  - MTD (dose escalation phase) of TAK-659 when administered with each of the combination drugs.
  - RP2D (dose escalation phase) of TAK-659 when administered with each of the combination drugs.
- Secondary Endpoints:
  - TAK-659 PK parameters, including maximum observed concentration (C_{max}), time of first occurrence of C_{max} (T_{max}), and area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) by dose escalation cohort.
  - Objective response rate (ORR) by IWG.
  - Duration of response (DOR).
  - Time to progression (TTP).

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- Progression-free survival (PFS) (for patients in the Cohort B expansion phase).

- Additional Endpoints:
  - Safety parameters, including percentage of patients with AEs, percentage of patients with Grade ≥3 AEs, percentage of patients with serious adverse events (SAEs), percentage of patients who discontinued due to AEs, clinically significant laboratory values, and clinically significant vital sign measurements.
  - Other TAK-659 PK parameters, including apparent oral clearance, peak-trough ratio, accumulation ratio, and trough concentration by dose escalation cohort.

- Exploratory Endpoints:

CCI [redacted]

Statistical Considerations:

Dose escalation will be conducted according to a standard 3 + 3 dose escalation schema for each of the 5 cohorts. Approximately 12 dose-limiting toxicity (DLT)-evaluable patients from each of the 5 cohorts will participate in the dose escalation phase of the study. Dose escalation will continue until the TAK-659 MTD is reached or until TAK-659 100 mg QD (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified based on the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. The escalation of each of the combination cohorts is independent of the other cohorts.

Sample Size Justification: The dose escalation phase of this study will use a 3 + 3 design. With the exception of bendamustine, each combination drug's dose will be the dose according to the manufacturer's label. The dose of bendamustine will be based on its use in previous combination studies [3,4]. In the dose escalation phase, 9 to 12 DLT-evaluable patients from each of Cohorts A to E will be recruited based on 2 planned dose levels of TAK-659. A dose lower than 60 mg QD (eg, 40 mg QD) or intermittent QD dosing schedules (eg, 7 days on followed by 7 days off or 14 days on followed by 7 days off) may be evaluated in Cohort B, if appropriate. As a result, the actual number of patients to be enrolled into Cohort B will be increased accordingly. Twelve additional patients with FL or MZL will be recruited into Cohort B for the safety expansion phase; no patients from Cohorts A, C, D, or E will be recruited for the safety expansion phase since the sponsor has closed enrollment into these cohorts. Assuming a 10% dropout rate, approximately 40 patients in Cohort B, and 14 patients each in Cohorts A, C, D, and E will be recruited. The total sample size for this study will be approximately 96 patients.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, 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.

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3.3 List of Abbreviations

Abbreviation	Term
ΔAUC	change in area under the concentration-time curve
5-HT3	5-hydroxytryptamine 3
ABC	activated B-cell
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid 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	area under the concentration-time curve
AUC_{τ}	area under the concentration-time curve during a dosing interval
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BID	twice daily
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CO_2	carbon dioxide
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interactions
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC_{50}	concentration producing half-maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

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Abbreviation	Term
EMA	European Medicines Agency
EOT	end of treatment
FDA	[United States] Food and Drug Administration
FDG	fluoro-2-deoxy-D-glucose
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
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activating motif
IV	intravenous(ly)
IWG	International Working Group
LDH	lactate dehydrogenase
MAD	maximally administered dose
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
ORR	overall response rate
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic(s)
PLT	platelets
PO	per os; by mouth (orally)

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Abbreviation	Term
PR	partial response
PTE	pretreatment event
Q2W	every 2 weeks (14 days)
QD	quaque die; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcF	Fridericia's corrected QT interval
RA	rheumatoid arthritis
RBC	red blood cell
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
SUV	standardized uptake value
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	time of first occurrence of C_{max}
TTP	time to progression
ULN	upper limit of the normal range
US	United States
USPI	United States Package Insert
WBC	white blood cell
WHO	World Health Organization
WM	Waldenström macroglobulinemia
WOCBP	women of childbearing potential

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

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4.0 INTRODUCTION

4.1 Background

4.1.1 Diseases Under Study

Non-Hodgkin lymphoma (NHL), is the most common hematologic malignancy and consists of numerous subtypes [5]; it is one of the most common cancers in the United States (US), accounting for about 4% of all cancers [6]. In 2018, an estimated 74,680 new cases of NHL are expected to be diagnosed in the US, and an estimated 19,910 people will die of this disease [7]. The two most common types of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). DLBCL accounts for about 1 of every 3 lymphomas, and FL accounts for about 1 of every 5 lymphomas in the US [8].

The immunochemotherapy regimen R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone with rituximab) is the standard treatment for patients with newly diagnosed DLBCL [5,6]. This regimen results in complete remission in approximately 65% to 75% of first-line patients with DLBCL. It is considered curative in a subset of patients, with a cure rate of >50% [7,8]. However, DLBCL is highly heterogeneous in histology, clinical behavior, and underlying biology, and therefore exhibits significant variation with regard to outcome after therapy.

High-dose chemotherapy, including salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), and autologous stem cell transplant (ASCT) are the treatments 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.

Follicular lymphoma (FL) is the most common indolent NHL in the Western hemisphere, representing 20% of NHL cases [9]. Randomized clinical trials have demonstrated that the addition of rituximab to standard chemotherapy induction has improved overall survival. Maintenance rituximab strategies can improve progression-free survival (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 [10].

4.1.2 Study Drug

4.1.2.1 TAK-659

TAK-659 is a small molecule that inhibits spleen tyrosine kinase (SYK) and FMS-like tyrosine kinase 3 (FLT3) and is currently under development for the treatment of patients with advanced malignancies. TAK-659 inhibits SYK- and FLT3-purified enzymes with a concentration producing 50% inhibition (IC_{50}) of 3.2 nM and 4.6 nM, respectively. TAK-659 demonstrated a more than 50-fold selectivity for SYK over 290 other protein kinases screened. In cultured

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human tumor cells, TAK-659 potently inhibited SYK activity in hematopoietic-derived cell lines (Section 4.1.3). TAK-659 is currently being investigated as a single agent in trials of patients with NHL and acute myelogenous leukemia (AML), as well as a combination agent in patients with lymphoma and solid tumors.

4.1.2.2 Bendamustine

Bendamustine is a bifunctional mechlorethamine derivative that forms covalent bonds with electron-rich nucleophilic moieties, resulting in intrastrand DNA crosslinks. These crosslinks can lead to cell death via several pathways in both quiescent and dividing cells. Bendamustine is indicated for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell NHL that has progressed during or within 6 months after treatment with rituximab or a rituximab-containing regimen [11]. Bendamustine in combination with rituximab has been used as second-line (or greater) therapy for patients with DLBCL.

4.1.2.3 Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen on the surface of pre-B and mature B lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Rituximab is indicated for the treatment of NHL; CLL; rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately to severely active RA who have inadequate response to 1 or more tumor necrosis factor antagonist therapies; and granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis in adult patients in combination with glucocorticoids [12]. Moreover, rituximab is indicated for previously untreated DLBCL in combination with CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone) or other anthracycline-based regimens.

4.1.2.4 Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor that kills cells undergoing DNA synthesis and blocks progression of the cells through the G1/S-phase boundary. Gemcitabine is indicated in combination with carboplatin for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy; in combination with paclitaxel for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated; in combination with cisplatin for the treatment of non-small cell lung cancer; and as a single-agent for the treatment of pancreatic cancer [13]. Gemcitabine has been used in second line (or greater) chemotherapy regimens for patients with relapsed/refractory DLBCL [14].

4.1.2.5 Lenalidomide

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide is indicated in the US in combination with dexamethasone for the treatment of multiple myeloma, for the treatment of transfusion-dependent anemia due to low- or intermediate-1–risk myelodysplastic syndromes associated with

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a deletion 5q abnormality with or without additional cytogenetic abnormalities, and for the treatment of mantle cell lymphoma (MCL) that has relapsed or progressed after 2 prior therapies, 1 of which included bortezomib [15].

4.1.2.6 Ibrutinib

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Ibrutinib is indicated for the treatment of MCL and CLL after at least 1 prior therapy, CLL with 17p deletion, and Waldenström macroglobulinemia (WM) [16].

4.1.3 Nonclinical Experience

4.1.3.1 Nonclinical Pharmacology Experience With TAK-659

TAK-659 is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FLT3. SYK is a nonreceptor tyrosine kinase with SH2-binding domains that binds to phosphorylated immunoreceptor tyrosine-based activation-motifs (ITAMs) located within receptors found on B and T cells and certain NK cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells, and abnormal function of SYK has been implicated in NHL, including FL, DLBCL, and MCL.

TAK-659 inhibits SYK-purified enzyme with an IC_{50} of 3.2 nM and a concentration producing half-maximal response (EC_{50}) ranging from 25 to 400 nM in sensitive cell systems. Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models, including the OCI-Ly10 model, an 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 FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including bendamustine, gemcitabine, lenalidomide, and ibrutinib. All combination drugs were given concomitantly in nonclinical studies.

Refer to the TAK-659 IB for additional information.

4.1.3.2 Nonclinical Pharmacology Experience With Combination Drugs

Bendamustine is a standard-of-care agent used in combination with rituximab as a second-line (or greater) therapy to treat patients with DLBCL. TAK-659 (60 mg/kg once daily [QD]) in combination with bendamustine (1 mg/kg twice weekly) in the OCI-Ly10 model resulted in significant antitumor activity with tumor growth inhibition (TGI) of 78.6% (change in area under the concentration-time curve [ΔAUC], $p<0.001$) when compared with vehicle. This combination resulted in additive antitumor activity in the OCI-Ly19 GCB DLBCL model where TAK-659

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(60 mg/kg QD) and bendamustine (2 mg/kg twice weekly) resulted in TGI of 52.1% (ΔAUC, $p<0.01$).

Gemcitabine HCl is a nucleoside analogue that primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. In DLBCL, gemcitabine is used to treat relapsed and refractory patients. TAK-659 has shown synergistic antitumor activity when combined with gemcitabine in nonclinical models of DLBCL. In the TMD8 model, TAK-659 (60 mg/kg QD) in combination with gemcitabine (5 mg/kg, every 3 days times 4) achieved significant antitumor activity with TGI of 96.7% (ΔAUC, $p<0.001$), demonstrating enhanced therapeutic potential over single-agent treatment. This combination was found to be additive in the OCI-Ly10 model with TGI of 90.6% (ΔAUC, $p<0.001$).

Lenalidomide is an immunomodulatory agent that has been shown to modulate different components of the immune system by altering cytokine production, regulating T-cell costimulation, and augmenting the NK cell cytotoxicity. The immunomodulatory properties of lenalidomide are implicated in its clinical efficacy and provide a rationale for combination with TAK-659. Combination of these agents in nonclinical studies has shown strongly additive tumor inhibition in the OCI-Ly10 DLBCL model. TAK-659 (60 mg/kg QD) in combination with lenalidomide (10 mg/kg QD) resulted in TGI of 73.1% (ΔAUC, $p<0.001$).

Ibrutinib is an inhibitor of BTK that is approved in CLL, MCL, WM, and marginal zone lymphoma and is currently in clinical trials for DLBCL. It is hypothesized that targeting BTK, which lies downstream of SYK, in combination with SYK inhibition could lead to a more pronounced response in hematologic malignancies. In nonclinical animal models of DLBCL, the combination of TAK-659 (60 mg/kg QD) with ibrutinib (6 mg/kg QD) has shown synergistic antitumor activity. In the OCI-Ly10 ABC DLBCL model, TAK-659 in combination with ibrutinib was found to have significant antitumor activity with TGI of 68.8% (ΔAUC, $p<0.001$) when compared with vehicle, resulting in a statistically significant therapeutic advantage over single-agent treatments.

Overall, data from nonclinical sources support the potential for TAK-659 to be an effective agent in treating patients with relapsed or refractory DLBCL in combination with bendamustine, gemcitabine, lenalidomide, or ibrutinib.

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). All 7 studies are ongoing.

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

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Table 4.a Overview of TAK-659 Clinical Studies

Protocol No. / Status	Study Design and Population	Dosing Regimen
C34001/ Ongoing	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; RP2D of 100 mg QD further explored in patients with lymphoma during dose expansion.
C34002/ Ongoing	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; MTD or RP2D not yet defined.
C34003/ Ongoing	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 is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg. For patients participating in the 2-week monotherapy run-in with TAK-659, the first dose will be on Cycle 1 Day 15.
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. *Combination Agents:* 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. 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. Gemcitabine: 1000 mg/m^2 IV infusion over 30 min on Days 1 and 8 of each 21-day cycle. Lenalidomide: 25 mg PO QD for Days 1-21 of each 28-day cycle. Ibrutinib: 560 mg PO QD of a 28-day cycle.

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

Protocol No. / Status	Study Design and Population	Dosing Regimen
C34007/Ongoing	Open-label, multicenter, 2-part, phase 1 study in East Asian adult patients, including a dose escalation in patients with NHL and an expansion in patients with DLBCL	TAK-659: Starting dose of 60 mg QD; dose will be escalated to 100 mg QD and will then follow 20 mg increments until MTD and/or RP2D is reached. Expansion phase will use RP2D.
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: planned 60 or 100 mg PO QD, 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.

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 Pharmacokinetics 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.

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4.1.5 Benefits and Risks

4.1.5.1 Potential Benefits and Risks of TAK-659

Potential Benefits of TAK-659

Clinical benefit has been observed in Study C34001. Response data were available for 85 patients (11 solid tumor, 58 DLBCL, 12 indolent NHL, and 4 CLL) as of 22 October 2017 in Study C34001. Among response-evaluable patients with solid tumors, 1 patient (9%) experienced a partial response (PR) and 1 patient (9%) had a response of stable disease (SD) at the time of the data cutoff. Among response-evaluable patients with lymphoma DLBCL, best responses of CR and PR were reported for 11 and 6 patients, respectively. Of the 17 patients with DLBCL who responded, 2 had transitioned to stem cell transplant before the data cutoff; 39 patients with DLBCL were still receiving study drug as of the data cutoff. Ten patients had a best response of SD, and 31 patients experienced progressive disease (PD). Among the 4 response-evaluable patients with CLL, 2 patients achieved PR and 2 had SD. Nine patients with indolent lymphomas responded to treatment with TAK-659. Three patients achieved a CR, 6 patients achieved PR, and 2 patients had SD.

Potential Risks From Nonclinical Studies in Dogs and Rats

- 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.

Potential Risks Based on Clinical Observations

- Based on data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In clinical studies to date, asymptomatic lipase elevations are reported commonly (≥10%). Patients in Study C34005 will have frequent monitoring of lipase and amylase as outlined in the Schedules of Events (Appendix A).

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- 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 potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.
- There have been occurrences of opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PJP), in some patients who had fever. These patients had other underlying conditions that made them prone to 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 treatment-emergent adverse event (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 TEAE (26%) and the most frequently reported SAE (15%). Cytomegalovirus (CMV) infection (20%) and sepsis (17%) were also frequently reported TEAEs. Sepsis (17%) and pneumonia (15%) were the most frequently reported Grade ≥3 TEAEs.

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

4.1.5.2 Potential Benefits and Risks of Combination Drugs

The benefits and risks associated with the administration of bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib should be referenced in accordance with their respective US Package Inserts (USPIs) [11-13,15-17] or applicable labeling.

TAK-659 has been investigated in combination with other agents in Studies C34003, C34005, and C34008, and preliminary activity has been observed (see TAK-659 IB). The combination of TAK-659 and other agents in this study (bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib) may lead to exacerbation of known toxicities of single-agent administration for each agent, and possibly the occurrence of new toxicities that have not been identified with the single agents.

Potential Overlapping Toxicities for the Combination of TAK-659 and Combination Drugs

Because the study is ongoing, and the safety data are limited, no identified risks for each of the combination agents in this study have been confirmed. Expectedness will be assessed using the respective approved reference safety information (RSI).

Drug-Drug Interaction Risk Assessment for the Combination of TAK-659 and Combination Drugs

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 P-glycoprotein (P-gp) and is metabolized by cytochrome P450 (CYP) 3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.40%, respectively. Consequently,

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there is a potential risk for TAK-659 PK to be altered by drugs that are strong CYP3A inhibitors or inducers or P-gp inhibitors or inducers.

Assessment of TAK-659 as Victim of DDIs

Based on data included in their respective USPIs [11-13,15-17] or applicable labeling, bendamustine, rituximab, gemcitabine, and lenalidomide are not expected to inhibit or induce CYP3A or P-gp at clinically relevant doses; therefore, it is unlikely for co-administration of these agents to cause alterations in TAK-659 PK.

However, at clinically relevant doses, ibrutinib has the potential to inhibit the efflux transporter P-gp in the gastrointestinal (GI) tract at higher local concentrations that may be achieved after PO administration. Thus, the systemic exposures of oral narrow therapeutic index P-gp substrates may be increased upon co-administration of ibrutinib because of decreased intestinal efflux and increased bioavailability of the oral P-gp substrate. Because in vitro data indicate that TAK-659 is a P-gp substrate, there is a theoretical risk of increased TAK-659 systemic exposure with ibrutinib co-administration (gut P-gp inhibitor) relative to TAK-659 administration alone. Based on current literature, the majority of clinical DDIs due to P-gp inhibition are associated with approximately 2-fold or lower increases in the exposures of P-gp substrates.

Assessment of TAK-659 as Perpetrator of DDIs

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 breast cancer resistance protein (BCRP) in Caco-2 cells at concentrations up to 100 μM. When these in vitro findings are viewed in context of the C_{max} observed in patients with lymphoma at the single-agent MTD of 100 mg QD (217 ng/mL or 0.63 μM), there is low risk for TAK-659 to cause DDIs via induction or inhibition of CYP enzymes, P-gp, or BCRP. Considering this information and the major determinants of clearance for all combination drugs (bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib), it is unlikely that TAK-659 will affect their PK when administered in combination.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for the Combination of TAK-659 + Combination Drugs

TAK-659 is an orally bioavailable, potent and reversible inhibitor of SYK and FLT3 and is currently under development for the treatment of patients with advanced malignancies (eg, NHL). SYK is a nonreceptor tyrosine kinase with SH2-binding domains that bind to phosphorylated ITAMs located on B and T cells and certain NK cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells and abnormal

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function of SYK has been implicated in NHL, including FL, DLBCL, and MCL. TAK-659 inhibits SYK purified enzyme with an IC_{50} of 3.2 nM and an EC_{50} ranging from 25 to 400 nM in sensitive cell systems.

Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models including the OCI-Ly10 model, an ABC-DLBCL model; the OCI-Ly19 model, a GCB-DLBCL model; the PHTX-95L model, a primary human DLBCL model; the RL FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including gemcitabine, bendamustine, ibrutinib, and lenalidomide.

Early signs of clinical activity of TAK-659 have been observed in the first-in-human (FIH) Study C34001 in patients with multiple subtypes of NHL. In this study, response data were available for 85 patients (11 solid tumor, 58 DLBCL, 12 iNHL, and 4 CLL). Among response-evaluable patients with solid tumors, 1 patient (9%) had experienced a PR. Among response-evaluable patients with DLBCL, best responses of CR and PR were reported for 11 and 6 patients, respectively. Clinical activity in responding DLBCL patients was achieved independent of cell of origin subtype (GCB or non-GCB) or disease history (de novo or transformed) [18]. Refer to the TAK-659 IB for detailed clinical information.

Gemcitabine HCl is a nucleoside analogue that primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. TAK-659 has shown synergistic antitumor activity when combined with gemcitabine in nonclinical models. Ibrutinib is an inhibitor of BTK that is approved in CLL, MCL, WM, and marginal zone lymphoma and is currently in clinical trials for DLBCL. It is hypothesized that targeting BTK, which lies downstream of SYK, in combination with SYK inhibition could lead to a more pronounced response in hematologic malignancies. In nonclinical animal models, the combination of TAK-659 with ibrutinib has shown synergistic antitumor activity. Bendamustine is a standard-of-care agent used in combination with rituximab as a second-line therapy to treat patients with NHL. Bendamustine has also shown synergistic TGI when combined with TAK-659. Lenalidomide is an immunomodulatory agent that has been shown to modulate different components of the immune system by altering cytokine production, regulating T-cell co-stimulation, and augmenting the NK cell cytotoxicity. The immunomodulatory properties of lenalidomide are implicated in its clinical efficacy and provide a rationale for combination with TAK-659.

Nonclinical combination of these agents has shown strongly additive tumor inhibition in mouse models. Overall, data from nonclinical sources support the potential for TAK-659 to be an effective agent in treating patients with relapsed or refractory NHL in combination with bendamustine, gemcitabine, lenalidomide, or ibrutinib.

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4.2.2 Rationale for Dose and Schedule Selection

4.2.2.1 Rationale for the Dose and Schedule of TAK-659

TAK-659 has been evaluated as a single agent given PO on a continuous daily dosing schedule in its FIH dose escalation study (C34001) in patients with advanced solid tumors or lymphoma. Four dose levels (60, 80, 100, and 120 mg QD) have been evaluated in Study C34001, and the MTD has been determined to be 100 mg QD. Following the safety expansion of the 100 mg cohort, Study C34001 is currently in the dose expansion phase, evaluating the efficacy, safety, and tolerability of TAK-659 administered at the 100 mg dose level in 5 different cohorts of B-lymphocyte malignancies. Early signs of clinical activity in lymphoma have been demonstrated across all doses evaluated.

Currently, TAK-659 is being evaluated as in combination with nivolumab (Study C34003) and venetoclax (Study C34008). Based on the dose escalation experience with TAK-659 in Studies C34001, C34003, and C34008, dosing of TAK-659 will escalate in 20 mg increments up to 100 mg QD provided that the safety and tolerability of the 60 mg QD dose is demonstrated. Alternative dose regimens (eg, intermittent QD dosing of 7 days on followed by 7 days off, or 14 days on followed by 7 days off), or dose levels below the starting dose of 60 mg (eg, 40 mg) may be evaluated based on safety, tolerability, and preliminary PK and efficacy data, if available, following agreement between investigators and the sponsor. The dose of TAK-659 cannot be escalated beyond 100 mg, which is the MTD for single-agent TAK-659 in solid tumors and lymphoma.

In this dose escalation study, the starting dose of TAK-659 will be 60 mg QD in combination with a fixed dose regimen of each combination drug. Dose escalation of TAK-659 will follow a standard 3 + 3 escalation scheme.

4.2.2.2 Rationale for the Dose and Schedule of Combination Drugs

The dose and schedule at which bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib will be administered will be in accordance with their respective USPIs [11-13,15-17] or applicable labeling, unless otherwise specified. The dose of bendamustine (90 mg/m^2) is based on its use in previous combination studies with rituximab in both indolent NHL and DLBCL [3,4].

4.2.3 Rationale for PK Assessments

The primary aim of PK sampling in this study is to compare exposures of TAK-659 following co-administration with each combination drug with exposures observed following single-agent administration. Specifically, PK data from this combination study will be compared with historical single-agent exposures observed in Study C34001 to determine whether there are clinically meaningful differences in TAK-659 PK between the single-agent and combination settings in patients with lymphoma. In the dose escalation phase, intensive PK samples will be collected from all patients during Cycle 1, as detailed in Appendix A, Table 3. In the safety expansion part, sparse PK samples will be collected (refer to Appendix A, Table 4). Plasma PK

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

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to determine the MTD or RP2D for TAK-659 when administered in combination with each of the combination drugs (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib).

5.1.2 Secondary Objectives

The secondary objectives are:

- To characterize the plasma PK of TAK-659 in each of the 5 cohorts.
- To observe the preliminary efficacy of different combination drugs with TAK 659 (Cohorts A-E) in patients with advanced NHL who have relapsed and/or are refractory after ≥1 prior line of therapy (for patients in Cohort B expansion with FL/marginal zone lymphoma (MZL), ≤1 prior line of therapy).

5.1.3 Additional Objective

The additional objective is to evaluate the safety and tolerability of TAK-659 in each of the 5 cohorts.

5.1.4 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- MTD (dose escalation phase) of TAK-659 when administered with each of the combination drugs.
- RP2D (dose escalation phase) of TAK-659 when administered with each of the combination drugs.

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5.2.2 Secondary Endpoints

The secondary endpoints are:

- TAK-659 PK parameters, including C_{max}, T_{max}, and AUC_{τ} by dose escalation cohort.
- Overall response rate (ORR) by International Working Group (IWG).
- Duration of response (DOR).
- Time to progression (TTP).
- PFS (for patients in the Cohort B expansion phase).

5.2.3 Additional Endpoints

The additional endpoints are:

- Safety parameters, including percentage of patients with AEs, percentage of patients with Grade ≥3 AEs, percentage of patients with SAEs, percentage of patients who discontinued due to AEs, clinically significant laboratory values, and clinically significant vital sign measurements.
- Other TAK-659 PK parameters, including apparent oral clearance, peak-trough ratio, accumulation ratio, and trough concentration by dose escalation cohort.

5.2.4 Exploratory Endpoints

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[redacted]

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination drugs (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with advanced NHL after at least 1 prior line of therapy. The primary objective of the study is to determine the MTD or the RP2D of TAK-659 when administered with each of the combination drugs. Once enrolled in the study, patients will be assigned to 1 of 5 combination cohorts:

- Cohort A (TAK-659 + bendamustine).
- Cohort B (TAK-659 + bendamustine + rituximab).
- Cohort C (TAK-659 + gemcitabine).
- Cohort D (TAK-659 + lenalidomide).
- Cohort E (TAK-659 + ibrutinib).

This study comprises 2 phases: a dose escalation phase and a safety expansion phase. Patients in all 5 cohorts (Cohorts A-E) will participate in the dose escalation phase of the study.

During the dose escalation phase, the dose of TAK-659 will be escalated (planned 3 dose levels of escalation: 60, 80, and 100 mg) according to a 3 + 3 dose escalation scheme. The dose of oral TAK-659 will increase in 20 mg increments to a maximum of 100 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose levels below the starting dose of 60 mg QD (eg, 40 mg QD) or intermittent QD dosing schedules (eg, 7 days on followed by 7 days off, or 14 days on followed by 7 days off) also may be evaluated, if appropriate, in Cohort B. Dose escalation will continue until the MTD is reached, or until TAK-659 100 mg QD (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified based on the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond.

The doses of combination drugs will be administered at a fixed dose and regimen (see Section 8.3).

During the dose escalation phase, DLT-evaluable patients in each dose cohort will consist of patients who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The dose escalation decision is based on the DLT occurrences during Cycle 1 per the 3 + 3 escalation schema. Additionally, toxicity and tolerability beyond Cycle 1, available PK and pharmacodynamic data, and early signs of clinical activity will be taken into consideration in dose escalation decisions and final determination of the MTD and RP2D of TAK-659 with combination drugs in each of the cohorts. Based on the evolving data from the trial, an alternative dose escalation plan including dose, schedule, DLT evaluation period, and further expansion of a given cohort, may be subject to change following discussions and agreement between the investigators and the sponsor medical monitor.

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During the safety expansion phase of the study, approximately 12 additional patients with advanced FL or MZL will be added to Cohort B at the MTD/MAD/RP2D for further safety evaluation. PK samples will be collected at prespecified time points to characterize the PK of TAK-659 when administered with each of the combination drugs. No patients from Cohorts A, C, D, or E will enter the safety expansion phase of the study because effective 16 March 2018, the sponsor closed recruitment into Cohorts C, D, and E, and effective 16 October 2018, the sponsor closed recruitment into Cohort A.

Patients, including those who achieve a CR, may receive study treatment, for a maximum of 12 months, until they experience PD or unacceptable toxicities.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010 [3]. DLTs are defined in Section 8.2.

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-659 when administered in combination with each of the 6 combination drugs.

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[redacted]

Disease status will be assessed using the IWG [2] revised criteria for patients with malignant lymphoma, based on investigator assessment. Computed tomography (CT) scans (with contrast) of the chest, abdomen, and pelvis (neck should be included if appropriate) and fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) scans extending from neck to mid-thigh will be performed in all patients to follow the disease as indicated in the Schedule of Events (Appendix A, Table 1 and Table 2). Repeat FDG-PET scans will be performed during the study only when the screening FDG-PET scan is positive. For patients with a negative screening

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FDG-PET scan, additional scans may be performed on study if clinically indicated for occurrence of PD per local standard of care.

6.2 Number of Patients

It is expected that approximately 96 patients will be enrolled in this study from approximately 15 study centers in North America and Europe. Approximately 40 patients will be enrolled in Cohort B, and approximately 14 patients will be enrolled in each of Cohorts A, C, D, and E (Table 6.a). Enrollment is defined as the time of the initiation of the first dose of study drug.

Table 6.a Planned Number of Patients

Cohort	Total (~N) [a]	Dose Escalation (~N)	Safety Expansion (~N)
A	14	9-12	0 [b]
B	40	9-24 [c]	12
C	14	9-12	0 [b]
D	14	9-12	0 [b]
E	14	9-12	0 [b]

[a] Approximate enrolled number was based on the assumption of a 10% dropout rate.
[b] Effective 16 March 2018, enrollment into Cohorts C, D, and E was closed, and effective 16 October 2018, enrollment into Cohort A was closed. No patients from these 4 cohorts will enter into the safety expansion phase of this study.
[c] A dose lower than 60 mg QD or intermittent dosing schedules may be evaluated, if appropriate.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

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 study drug-related or possibly related toxicity.

The maximum duration of treatment, however, will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

At the conclusion of the study, participants who continue to demonstrate clinical benefit may be eligible to receive Takeda-supplied study drug. Study drug may be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of Takeda.

Takeda reserves the right to terminate access to Takeda supplied study drug if any of the following occurs: a) the benefit-risk profile is not favorable; b) the marketing application is rejected by responsible health authority; c) the study is terminated due to safety concerns; d) investigational agent(s) becomes commercially available or other access mechanism becomes

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available; e) development of the drug is suspended or ceased, or sponsor cannot adequately supply investigational agent; or f) appropriate therapeutic alternatives become available in the local market.

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

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the primary endpoint and authoring of a single, final CSR will be conducted after all patients enrolled in the study have had the opportunity to complete 6 cycles of treatment with study drug and be followed for 28 days or the start of subsequent anticancer therapy, whichever occurs first. In the Cohort B expansion phase, patients who discontinue treatment for any reason other than PD will continue to have PFS follow-up visits. 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 30 months.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

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

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Table 6.b Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Primary:		
• MTD (dose escalation phase) of TAK-659 when administered with each of the combination drugs.	Maximum dose that is determined to be safe and tolerable	Up to 6 months.
• RP2D (dose escalation phase) of TAK-659 when administered with each of the combination drugs.	The dose recommended for use in phase 2 studies based on the safety, tolerability, and preliminary PK and efficacy data (if available) obtained in phase 1 studies	Up to 6 months.
Secondary:		
• TAK-659 PK parameters, including C_{max}, T_{max}, and AUC_{τ} by dose escalation cohort.	Descriptive statistics for C_{max}, T_{max}, and AUC_{τ} for each dose group of each cohort in the PK population [b]	Up to 16 days.
• ORR by IWG	The proportion of patients in the response-evaluable population who achieved either CR or PR	Up to 6 months.
• DOR	The time from first CR/PR to PD or relapse in the response-evaluable population	Up to 6 months.
• TTP	Time from first dose to PD or relapse in the response-evaluable population	Up to 6 months.
• PFS	The time from the date of first study drug administration to the date of first documented PD or death due to any cause, whichever occurs first.	Up to 6 months.

AUC: area under the concentration-time curve; AUC_{τ}: AUC during a dosing interval; C_{max}: maximum observed concentration; CR: complete response; DOR: duration of response; MTD: maximum tolerated dose; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic(s); PR: partial response; RP2D: recommended phase 2 dose; t_{max}: time of first occurrence of C_{max}; TTP: time to progression.
[a] Time to last assessment for that endpoint for an individual.
[b] For Cohorts A-E in the dose escalation phase, on Cycle 1 Days 1 and 15.

6.3.4 Total Study Duration

It is anticipated that this study will last approximately 30 months.

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7.0 STUDY POPULATION

Patients must have a histologically or cytologically confirmed diagnosis of advanced NHL of any histology (with the exception of patients with WM and CLL), radiographically or clinically measurable disease with at least 1 target lesion per IWG criteria for malignant lymphoma [2], and must be refractory or relapsed after at least 1 prior line of therapy and have no effective standard therapy available per investigator's assessment. Patients must also be either treatment naïve to, relapsed/refractory to, or have experienced treatment failure due to other reasons with ibrutinib, idelalisib, or any other investigational BCR pathway inhibitors not directly targeting SYK.

7.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. In the dose escalation phase, histologically or cytologically confirmed diagnosis of advanced NHL of any histology (with the exception of patients with WM and CLL). In the safety expansion phase for Cohort B, only patients with advanced FL or MZL will be included.
3. Radiographically or clinically measurable disease with at least 1 target lesion per IWG criteria for malignant lymphoma [2].
4. In the dose escalation phase, patients who are refractory or relapsed after at least 1 prior line of therapy due to progression, intolerance, or physician/patient decision and for whom no effective standard therapy is available per the investigator's assessment. In the safety expansion phase for Cohort B in patients with FL or MZL, the prior line of therapy is limited to ≤1.
   a) Either treatment naïve to, relapsed/refractory to, or experienced treatment failure due to other reasons with ibrutinib, idelalisib, or any other investigational BCR pathway inhibitors not directly targeting SYK.
   b) Preinduction salvage chemotherapy and ASCT should be considered 1 therapy.
   c) Any consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 line of therapy with the preceding combination therapy. Maintenance antibody therapy should not be considered a line of therapy.
   d) For aggressive NHL (ie, DLBCL), single-agent anti-CD20 monoclonal antibody therapy should not be considered a line of therapy. Antibody therapy in patients with indolent NHL (ie, FL) given as a single agent after disease progression from a prior treatment should be considered a line of therapy.
   e) For patients with DLBCL transformed from indolent lymphoma, any treatment received for the indolent disease before the transformation to DLBCL will, in general, not count toward the 2 to 3 prior lines of therapy required for DLBCL in this study.

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f) Prior treatment with a regimen that includes the combination drug will not necessarily exclude a patient from that cohort if the investigator views treatment with that agent as appropriate. However, a patient who has a contraindication for a particular combination agent or who has been discontinued from prior therapy with a particular agent for toxicity will not be eligible for inclusion in that particular cohort.

5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and life expectancy of greater than 3 months (see Appendix D).
6. Patients must have adequate organ function, including the following:
   a) Adequate bone marrow reserve: absolute neutrophil count (ANC) ≥1000/μL, platelet count ≥75,000/μL (≥50,000/μL for patients with bone marrow involvement), and hemoglobin ≥8 g/dL (red blood cell [RBC] and platelet transfusion allowed ≥14 days before assessment).
   b) Hepatic: total bilirubin ≤1.5 times the upper limit of the normal range (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN.
   c) Renal: creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault equation (see Appendix E).
   d) Others:
      i. Lipase ≤1.5 × ULN and amylase ≤1.5 × ULN with no clinical symptoms suggestive of pancreatitis or cholecystitis.
      ii. Blood pressure Grade ≤1 (hypertensive patients are permitted if their blood pressure is controlled to Grade ≤1 by antihypertensive medications).
      iii. Fasting serum glucose level shall be controlled to 130 mg/dL during the screening period.
7. Female patients who:
   a) Are postmenopausal 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 F) 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 patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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e) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) at screening.

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 patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8. Female patients should not donate ova from the time of signing the informed consent through 180 days after the last dose of study drug.
9. Male patients should not donate sperm from the time of signing the informed consent through 180 days after the last dose of study drug.
10. Both men and women in Cohort B (TAK-659+bendamustine+rituximab) must practice contraception as described above from the time of signing of the informed consent form (ICF) through 12 months after the last dose of study drug.
11. Both men and women in Cohort D (TAK-659+lenalidomide) must adhere to the guidelines of the RevAssist program (US participants) or the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the study manual (all other participants who are not using commercial supplies).
12. 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.
13. Recovered (ie, Grade ≤1 toxicity) from the clinically significant reversible effects of prior anticancer therapy.

7.2 Exclusion Criteria

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

1. Central nervous system (CNS) lymphoma; active brain or leptomeningeal metastases, as indicated by positive cytology from lumbar puncture or CT scan/magnetic resonance imaging (MRI). Exceptions include those patients who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids, and do not have neurologic dysfunction that would confound the evaluation of neurologic and other AEs.
2. Known human immunodeficiency virus (HIV)-related malignancy.

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3. Known hypersensitivity (eg, anaphylactic and anaphylactoid reactions) to any particular combination drug and/or drug component will result in a patient being ineligible for inclusion in that particular cohort.
4. For patients in Cohort D (TAK-659 + lenalidomide), demonstrated hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.
5. History of drug-induced pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Life-threatening illness unrelated to cancer that could, in the investigator's opinion, make the patient not appropriate for this study.
7. Female patients who are lactating and breast-feeding or a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
8. 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.
9. Known HIV positive.
10. Known hepatitis B surface antigen positive, or known or suspected active hepatitis C infection.
11. Systemic anticancer treatment (including investigational agents) or radiotherapy less than 2 weeks before the first dose of study treatment (≤4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine).
12. Prior ASCT within 6 months or prior ASCT at any time without adequate hematopoietic recovery, defined by the entry criteria in the study, before Cycle 1 Day 1, or allogeneic stem cell transplant any time.
13. Any clinically significant comorbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active CNS disease, active infection, or any other condition that could compromise the patient's participation in the study.
14. Patients with any of the following cardiovascular conditions are excluded:
    a) Unstable angina or acute myocardial infarction within 12 months before starting study drug.
    b) Current or history of New York Heart Association Class III or IV heart failure (see Appendix G).

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c) Evidence of current, uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

d) Fridericia's corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the screening period.

e) Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that, in the opinion of the investigator, are considered to be clinically significant.

15. Lack of suitable venous access for the study-required blood sampling for TAK-659.

16. Use or consumption of any of the following substances:

a) Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, the use of these agents is not permitted during the study except in cases in which an AE must be managed (see Section 8.5). See Appendix H 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.

b) Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drug. In general, the use of these agents is not permitted during the study except in cases in which an AE must be managed (see Section 8.5). See Appendix H 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.

c) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are not permitted during the study.

17. Additionally, for patients in the ibrutinib combination arm (Cohort E), use or consumption of any of the following substances:

a) Medications or supplements that are known to be moderate 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 drugs. In general, the use of these agents is not permitted during the study for this combination except in cases in which an AE must be managed (see Section 8.5). See Appendix H for a nonexhaustive list of moderate CYP3A reversible inhibitors based on the US FDA Draft DDI Guidance.

b) Medications or supplements that are known to be moderate mechanism-based inhibitors or moderate inducers of CYP3A within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drugs. In general, the use of these agents is not permitted during the study for this combination except in cases in

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which an AE must be managed (see Section 8.5). See Appendix H for a nonexhaustive list of moderate CYP3A mechanism-based inhibitors or moderate CYP3A inducers based on the US FDA Draft DDI Guidance.

c) Seville oranges within 5 days before the first dose of study drugs and during the study.

18. Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.
19. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug.
20. 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.
21. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-659 including difficulty swallowing tablets or diarrhea Grade >1 despite supportive therapy.
22. Treatment with high-dose corticosteroids for anticancer purposes within 14 days before the first dose of TAK-659; daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.

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8.0 STUDY DRUG

8.1 Study Drug Administration

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

The dosing regimen for study drugs in each of the cohorts is outlined in the following sections.

8.1.1 Cohort A (TAK-659 + Bendamustine) Dosing Regimen

TAK-659 will be dosed PO QD in 21-day cycles. Bendamustine will be administered in the clinic in accordance with the Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling unless otherwise specified. The dose of bendamustine will be based on its use in previous combination studies [3,4]. Patients will receive 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of each 21-day cycle, up to 8 cycles. Monotherapy with TAK-659 is allowed beyond 8 cycles. On days on which both TAK-659 and bendamustine are administered, the TAK-659 dose will be administered first, followed by the bendamustine infusion (infusion to begin within 15 minutes after the TAK-659 dose) to maximize the overlap in exposures between the 2 drugs.

Please see Table 8.a for further information on the dosing schedule for each cycle in Cohort A.

Table 8.a Cohort A (TAK-659 + Bendamustine) Dosing Schedule

Cohort A	21-Day Cycle, Bendamustine Up to 8 Cycles, TAK-659 All Cycles																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
TAK-659	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bendamustine	X	X																			

8.1.2 Cohort B (TAK-659 + Bendamustine/Rituximab) Dosing Regimen

TAK-659 will be administered PO QD in each 21-day cycle. Bendamustine will be administered in the clinic in accordance with the Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling unless otherwise specified. The dose of bendamustine will be based on its use in previous combination studies [3,4]. Patients will receive 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of each 21-day cycle, up to 8 cycles. Rituximab will be administered in the clinic in accordance with local guidelines and the rituximab USPI [12] or applicable labeling. Patients will receive 375 mg/m^2 rituximab administered IV on Day 1 of each 21-day cycle, up to 8 cycles. Monotherapy with TAK-659 is allowed beyond 8 cycles. On days (ie, Day 1) in which all 3 agents (TAK-659, bendamustine, and rituximab) are given, TAK-659 should be administered first, followed by the bendamustine infusion (infusion to begin within 15 minutes after the TAK-659 dose) to maximize the overlap in exposures between the 2 drugs. After completion of the bendamustine infusion, the rituximab infusion should be administered. On days (ie, Day 2) in

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which only TAK-659 and bendamustine are administered, the TAK-659 dose will be administered first, followed by the bendamustine infusion (infusion to begin within 15 minutes after the TAK-659 dose) to maximize the overlap in exposures between the 2 drugs.

Please see Table 8.b for further information on dosing schedule for each cycle in Cohort B.

Table 8.b Cohort B (TAK-659 + Bendamustine/Rituximab) Dosing Schedule

Cohort B	21-Day Cycle, Bendamustine/Rituximab Up to 8 Cycles, TAK-659 All Cycles																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
TAK-659 [a, b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bendamustine	X	X																			
Rituximab	X																				

[a] For the TAK-659 QD continous dosing schedule only.
[b] The TAK-659 dosing schedule will be consistent with the intermittent QD dosing schedule (eg, skip dosing on Days 15 to 21 for the schedule of 14 days on followed by 7 days off).

8.1.3 Cohort C (TAK-659 + Gemcitabine) Dosing Regimen

TAK-659 will be administered PO QD in each 21-day cycle. Gemcitabine will be administered in the clinic in accordance with the gemcitabine USPI [13] or applicable labeling. Patients will receive 1000 mg/m^2 gemcitabine administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle. On days on which both TAK-659 and gemcitabine are administered, the TAK-659 dose will be administered first followed by the gemcitabine infusion (infusion to begin within 15 minutes after the TAK-659 dose) to maximize the overlap in exposures between the 2 drugs.

Please see Table 8.c for further information on dosing schedule for each cycle in Cohort C.

Table 8.c Cohort C (TAK-659 + Gemcitabine) Dosing Schedule

Cohort C	21-Day Cycle, All Cycles																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
TAK-659	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gemcitabine	X							X													

8.1.4 Cohort D (TAK-659 + Lenalidomide) Dosing Regimen

TAK-659 will be administered PO QD in each 28-day cycle. Lenalidomide will be administered in accordance with the lenalidomide USPI [15] or applicable labeling. Patients will receive 25 mg lenalidomide PO QD for 21 days, followed by a 7-day rest period, during each 28-day cycle. On days on which both TAK-659 and lenalidomide are administered, the lenalidomide dose should be administered within 15 minutes after the TAK-659 dose to maximize the overlap in exposure between the 2 drugs.

Please see Table 8.d for further information on dosing schedule for each cycle in Cohort D.

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Table 8.d Cohort D (TAK-659 + Lenalidomide) Dosing Schedule

Cohort D	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
TAK-659	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lenalidomide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							

8.1.5 Cohort E (TAK-659 + Ibrutinib) Dosing Regimen

TAK-659 will be administered PO QD in each 28-day cycle. Ibrutinib will be administered in accordance with the ibrutinib USPI [16] or applicable labeling. Patients will receive 560 mg ibrutinib PO QD in 28-day cycles. The ibrutinib dose should be administered within 15 minutes after the TAK-659 dose to maximize the overlap in exposures between the 2 drugs.

Please see Table 8.e for further information on dosing schedule for each cycle in Cohort E.

Table 8.e Cohort E (TAK-659 + Ibrutinib) Dosing Schedule

Cohort E	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
TAK-659	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ibrutinib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

8.1.6 Oral Drug Administration

Study drugs administered PO, including TAK-659, lenalidomide, and ibrutinib, 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/capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed doses of both oral drugs. Patients should swallow the tablets/capsules whole; the tablets/capsules should not be chewed, crushed, or manipulated in any way before swallowing. Administration of the tablets/capsules 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 clinic visit days, patients should be instructed to hold their dose until predose assessments are performed in the clinic, and a particular dosing sequence for the study drugs will be followed by the study staff per protocol. If a patient fails to take oral study drug(s) one day, or if a patient does not take the oral study drug(s) at their scheduled dosing time (±6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments to account for the missed dose on subsequent days, for example, by taking a double dose of study drug(s) on 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.

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If severe emesis prevents the patient from taking a dose of study drug(s), that dose will be skipped. If emesis occurs after study medication ingestion, patients should simply adhere to the dosing schedule and continue dosing at the next scheduled time with the prescribed dosage. Patients should not take a repeat dose following emesis after study medication ingestion. Patients should record the time of the emesis in their dosing diary (see the study manual).

In cohorts where both study drugs are administered PO (Cohort D: TAK-659 + lenalidomide and Cohort E: TAK-659 + ibrutinib), the combination drug dose should be administered within 15 minutes after the TAK-659 dose to maximize the overlap in exposures between the 2 drugs.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE version 4.03, effective 14 June 2010 [1]. These criteria are provided in the study manual. DLT is defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with TAK-659 when administered in combination with bendamustine ± rituximab, gemcitabine, lenalidomide, and ibrutinib. AEs in which the relationship to study drug cannot be ruled out should be considered possibly related to study drug.

- Hematologic toxicity:
  - Grade 4 neutropenia (ANC <500/µL) unresolved to Grade ≤1 (ANC >1500/µL) or baseline for more than 7 consecutive days in the absence of growth factor support.
  - Grade ≥3 neutropenia (ANC <1000/µL) with fever and/or infection, where fever is defined as an oral temperature ≥38.5ºC.
  - Grade 4 thrombocytopenia (<25,000/µL) unresolved to Grade ≤1 (>75,000/µL) or baseline for more than 7 consecutive days or a platelet count <10,000/µL at any time.
  - Grade ≥3 thrombocytopenia (<50,000/µL) with clinically significant bleeding.
  - Grade 4 anemia.
- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - Fatigue or arthralgia/myalgia that improve to Grade ≤2 within 7 days.
  - Grade ≥3 nausea and/or emesis that can be controlled to Grade ≤1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 (5-HT_3) antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Grade ≥3 diarrhea that can be controlled to Grade ≤1 or baseline in 7 days with optimal supportive therapy.
  - Asymptomatic Grade 3 amylase or lipase elevations that last ≤7 days.
  - Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3) considered not dose limiting following agreement between the sponsor and investigators.

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  - Isolated Grade ≥3 abnormalities of other laboratory parameters (other than electrolyte imbalances/abnormalities) that resolve to Grade ≤1 in ≤7 days without clinical sequelae or need for therapeutic intervention considered not dose-limiting following agreement between the sponsor and investigators.
  - Grade 3 rash lasting ≤7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.
  - Any other Grade 3 nonhematologic toxicity that can be controlled to Grade ≤1 or baseline in 7 days with appropriate treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor medical monitor.
- Inability to administer at least 75% of planned doses of TAK-659 within Cycle 1 due to treatment-related toxicity.
- Delay in the initiation of the subsequent cycle of therapy by more than 7 days due to study drug-related hematologic or nonhematologic toxicities.
- Other study drug-related nonhematologic toxicities Grade ≥2 that, in the opinion of the investigator, require a dose reduction or discontinuation of study treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor medical monitor.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment in this dose escalation study will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

Patients experiencing a DLT in Cycle 1 may continue in the study if they are deriving clinical benefit, but they will be administered reduced doses of TAK-659 and/or the combination agent as appropriate.

8.3 Dose Escalation Rules

The dose escalation phase of the study is designed to determine the DLTs and MTD and/or RP2D of TAK-659 when given in combination with bendamustine (± rituximab), gemcitabine, lenalidomide, or ibrutinib. Patients in Cohorts A to E will be dosed based on the planned 3 dose-level escalation for TAK-659 (Table 8.f) in each of the combination cohorts. The exact number of patients to be enrolled will depend on the actual number of dose-level cohorts required, which may deviate from the dose escalation plan based on toxicities and the PK results observed during the initial dose levels.

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The dose of the combination drugs will be as follows:

Cohort	Combination Study Drug	Dosage and Regimen
A	Bendamustine	90 mg/m^2 administered IV over 10 or 60 minutes (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 minutes (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 administered IV per local guidelines and labeling on Day 1 of each 21-day cycle, up to 8 cycles
C	Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes 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 each 28-day cycle

The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3 + 3 escalation scheme (see Figure 8.a), and dosing of TAK-659 will increase to 100 mg QD (Table 8.f) provided that the safety and tolerability of the 60 mg dose has been demonstrated.

1. If 0 of 3 patients experiences 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 at any dose level experience DLT, dosing 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 between the current and the previous dose level will be evaluated.

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

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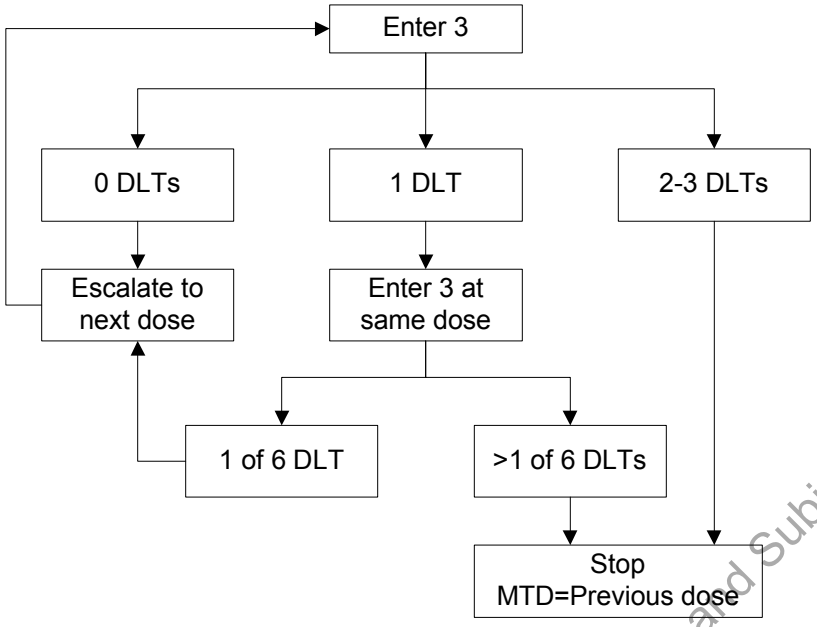
Figure 8.a Dose Escalation Algorithm



DLT: dose-limiting toxicity; MTD: maximum tolerated dose

During the dose escalation phase, 3 levels of dose escalation are planned for TAK-659: 60, 80, and 100 mg (Table 8.f), according to a 3 + 3 dose escalation scheme. The single-agent MTD for TAK-659 is 100 mg QD as established in the FIH dose escalation study of TAK-659 (C34001). Therefore, dose escalation of TAK-659 will not exceed 100 mg QD in this study. More conservative dose escalation, including de-escalation in 20 mg decrements from the starting dose of 60 mg QD of TAK-659 (eg, 40 mg QD) if that dose is determined to be not tolerable, expansion of an existing dose level, or an alternative regimen/schedule, are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety, for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659, or for adjustment based on the initial characterization of PK of TAK-659 when administered with the combination drugs.

Dose escalation continues until the MTD is reached, or until TAK-659 100 mg QD (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD/MAD, is identified based on the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 patients will be evaluated at the RP2D (the MTD or MAD or at a lower dose as determined) before making the dose decision. Further safety expansion of approximately 6 additional patients at the RP2D (up to 12 in total) is permitted to confirm the safety and tolerability of the combination dose of TAK-659 for each cohort.

Escalation will be based on safety as determined in Cycle 1. While the primary escalation schema is designed to determine a classical Cycle 1-based MTD, dose escalation may be halted

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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.

Table 8.f Planned Dose Levels of TAK-659 for Cohorts A to E

Dose Level	Dose (Unit)
1	60 mg
2	80 mg
3	100 mg [a]

[a] The maximum dose to be assessed is TAK-659 100 mg QD.

More conservative dose escalation, including evaluation of intermediate doses, dose de-escalation in 20 mg decrements from the starting dose of 60 mg QD if that is determined to be not tolerable, expansion of an existing dose level, and an alternative dose schedule/regimen are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity and preliminary PK and efficacy 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 during Cycle 1.

- For Cohorts A, B, and C, the minimum treatment and safety evaluation requirements are met if in Cycle 1, the patient has been treated with TAK-659 for ≥16 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1) plus 1 or 2 doses of the combination drug, and observed for ≥21 days following the dose on Cycle 1 Day 1 (unless DLT occurs before the end of the 21-day evaluation period), and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur.
- For Cohorts D and E, the minimum treatment and safety evaluation requirements are met if in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1), and 75% of the planned doses for each of the combination drugs (lenalidomide or ibrutinib, respectively), and observed for ≥28 days (unless DLT occurs before the end of the 28-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigator to conclude that a DLT did not occur.

Patients who do not meet these minimum requirements will be regarded as ineligible for DLT evaluation for the given dose cohort and may be replaced within the same cohort.

The decision to explore a lower dose of the combination drug should not solely be based on the safety and tolerability data of the combination drug in combination with TAK-659. The preliminary efficacy data should also be carefully examined in relation to available nonclinical data and knowledge of the clinical therapeutic dose range for the combination agent, and there must be some evidence that the effect of lowering the combination drug dose would most likely be compensated for by the combination effect with TAK-659, so that the level of single-agent combination drug activity most probably would not be compromised.

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8.4 Dose Modification Guidelines

In this dose escalation study, patients will be evaluated according to the Schedule of Events (Appendix A, Table 1 and Table 2) for each of the 5 cohorts for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE version 4.03, effective 14 June 2010 [1]. The causal relationship of each AE should be assessed in relation to TAK-659 and to the combination agent(s) in each cohort so that dose modifications can be made accordingly. Administration and dose adjustment of bendamustine (Cohort A), bendamustine ± rituximab (Cohort B), gemcitabine (Cohort C), lenalidomide (Cohort D), and ibrutinib (Cohort E) will follow applicable prescribing information, the guidance on dose modification (Section 8.4), and the guidance on the management of clinical events (see Section 8.8). Minimum re-treatment requirements described in the bendamustine and gemcitabine prescribing information must be met before starting the next cycle or dose of bendamustine and gemcitabine treatment in Cohorts A, B, and C, respectively (see Section 8.4.3). Dose modification guidelines for hematologic and nonhematologic toxicities are described below for study drugs in each of the combination cohorts based on the type and severity of AEs, causality determination by investigators, and safety and tolerability profiles of each of the study drugs. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

Per the dose modification guidelines, patients who have the study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE but may either maintain the same dose level or have doses of study drug reduced (dose reduction) by at least 1 dose level. Dose reduction levels for TAK-659 are presented in Table 8.g. When a dose reduction of TAK-659 occurs, the TAK-659 dose will be reduced to the next lower dose that has been established as a safe dose. The dose reduction of TAK-659 will, in general, follow a decrement of 20 mg. If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 may be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of TAK-659. Up to 2 dose-level reductions of TAK-659 due to AEs are generally recommended. If more than 2 dose-level reductions of TAK-659 are needed to manage TAK-659-related AEs, discontinuation of treatment should be considered unless the treating physician, in consultation with the sponsor, feels the patient may benefit from continued study treatment after resolution of AEs to Grade ≤1 or baseline, or a level (must be Grade ≤2) that is determined to be acceptable by the investigators based on benefit-risk assessment. Dose reduction for other combination agents is allowed per corresponding prescription information and clinical practice guideline.

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

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recommended for LDH. For management of toxicities on study, dose modification guidelines should be closely followed. However, based on 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.

Table 8.g Dose Reduction Levels for TAK-659

Dose Reduction Levels	Dose (Unit)
Planned dose	60, 80, or 100 mg
(-) 1 dose level	Planned dose minus 20 mg
(-) 2 dose levels	Planned dose minus 40 mg

Dose reduction levels for bendamustine, gemcitabine, lenalidomide, and ibrutinib are described in Table 8.h for AEs that are attributed to each of the combination agents. Rituximab will be maintained at the same dose in Cohort B.

Table 8.h Dose Reduction Levels for TAK-659 Combination Drugs

Dose Reduction Levels	Bendamustine	Rituximab	Gemcitabine	Lenalidomide	Ibrutinib
Planned dose	90 mg/m^2	375 mg/m^2	1000 mg/m^2	25 mg	560 mg
(–) 1 dose level	60 mg/m^2	Not applicable	750 mg/m^2	20 mg	420 mg
(–) 2 dose level	30 mg/m^2	Not applicable	500 mg/m^2	15 mg	280 mg

If the dose of 1 study drug in a combination regimen is delayed because of toxicity attributed to its use, the dose of the other study drug in the combination regimen is to be administered as scheduled.

8.4.1 Intrapatient Dose Escalation

Once the RP2D of TAK-659 is determined, all patients who have received TAK-659 and another combination agent at a dose lower than the RP2D of TAK-659 for a minimum of 2 cycles may dose escalate to the RP2D of the assigned treatment arm in the absence of PD or unacceptable treatment-related toxicity at the investigator's discretion and with the sponsor's approval. Patients for whom an increase in the dose of TAK-659 is being considered must have treatment-related AEs resolved to Grade ≤1 or baseline or to a level that is acceptable to the investigators (nonhematologic toxicity must be Grade ≤2, and hematologic toxicities must be less than the minimum requirement for starting a new cycle of treatment).

8.4.2 Intrapatient Dose Reduction (Cycle 1)

Intrapatient dose reductions of TAK-659 are not permitted in Cycle 1 during dose escalation unless the patient experiences a DLT attributed to TAK-659. DLT is defined in Section 8.2. If a patient experiences a DLT during Cycle 1, treatment should be held and the event counted

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toward the assessment of MTD for the given cohort. Patients experiencing a DLT in Cycle 1 may continue in the study upon resolution of the toxicity; however, the dose of TAK-659 (in combination with other combination agents) will be reduced by at least 1 dose level (or reduced by a 20 mg decrement if the patient is receiving the first dose level). Patients who receive a reduced dose of TAK-659 during Cycle 1 for reasons other than DLT will be replaced for DLT evaluation and dose escalation. Dose delay and dose reduction of any of the combination drugs, and dose modification, are allowed in Cycle 1 (see Section 8.4 and Section 8.4.3, which include bendamustine and gemcitabine retreatment criteria). Frequency of dose delay and reduction of other combination agents will be taken into account in determining the RP2D for TAK-659 when administered in combination with these agents.

8.4.3 Retreatment Criteria for Cohorts A, B, and C (Bendamustine or Gemcitabine)

Per the prescribing information for bendamustine and gemcitabine, the patient must meet the following retreatment criteria before starting the next dose of bendamustine (Cohorts A and B) or gemcitabine (Cohort C):

a) ANC ≥1000/μL.

b) Platelet count ≥75,000/μL.

For patients treated with bendamustine (±rituximab) in combination with TAK-659 (Cohorts A and B), 1 dose of 90 mg/m^2 bendamustine is given on Days 1 and 2 in 21-day cycles. If a patient does not meet the bendamustine retreatment criteria, the next cycle of bendamustine dosing should be delayed for 1 week while supportive care is given based on the local standard practice or as specified in Section 8.9.5. The patient should be re-evaluated within 7 days to determine whether the criteria for bendamustine re-treatment have been met. If the criteria have not been met, further delay of the next cycle of bendamustine and re-evaluation of bendamustine retreatment criteria will occur at maximally weekly intervals until all retreatment criteria are satisfied. Dose modification guidelines will be followed to determine whether the dose of bendamustine will be maintained or reduced when bendamustine dosing is resumed.

For patients treated with TAK-659 + gemcitabine (Cohort C), 2 doses of 1000 mg/m^2 gemcitabine will be given on Day 1 and Day 8 in 21-day treatment cycles. If the patient does not meet retreatment criteria for gemcitabine before Day 1 dosing in a given cycle, the start of the cycle will be delayed. The patient should be re-evaluated within 7 days to determine if gemcitabine retreatment criteria are met. If the re-treatment criteria are not met for the Day 8 dosing of gemcitabine, the Day 8 dose will be delayed to Day 15 (provided that all re-treatment criteria are met on Day 15). In this case, there will still be an off week before the start of the next cycle. If further delay is needed, the second dose of gemcitabine will be withheld, and gemcitabine will be resumed in the next cycle.

Discontinuation of study treatment should be considered if, because of lack of adequate recovery of the toxicities, there is a delay of a new cycle (due to Day 1 dosing delay for Cohorts A, B, or C) for ≥21 days (≥3 weeks), or a failure to resume the next cycle due to a delay of Day 8 gemcitabine dosing (for Cohort C only) for ≥21 days (≥3 weeks) after the initial delay. Continued treatment may be considered in the case of investigator-determined clinical benefit

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and discussion with the sponsor project clinician. However, study treatment may be resumed only after the re-treatment criteria are fully met. If a delay of ≥14 days (≥2 weeks) is required for resolution of toxicities before meeting the re-treatment criteria, dose reduction of bendamustine and gemcitabine to the next lower level should be considered (Table 8.h).

If the toxicities that result in failure to meet the bendamustine or gemcitabine re-treatment criteria are determined to be related to bendamustine or gemcitabine and not to TAK-659, patients should continue to receive TAK-659 according to the planned dose and regimen. If, in the investigator's opinion, TAK-659 contributes to the toxicities (related or possibly related) that lead to not meeting bendamustine or gemcitabine retreatment criteria, dose delay or modification of TAK-659 should be considered per the dose modification guidelines in Section 8.4.

8.4.4 Dose Modification for Hematologic and Nonhematologic Toxicity

Decisions regarding which study drug requires dose modification will be dependent upon the toxicity, its onset, and its time course. The causal relationship of any reported events (AEs or SAEs) should be assessed by the investigator in relation to TAK-659 and in relation to the combination drug (bendamustine ±rituximab, gemcitabine, lenalidomide, or ibrutinib). If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines and the causal relationship to 1 or both study drugs. Guidelines for dose modifications for hematologic and nonhematologic toxicity for each study Cohort (A-E) are presented in Table 8.i to Table 8.l. After discussion between the investigator and the Takeda project clinician, alternative dose modifications may be recommended to maximize exposure of study treatment while protecting patient safety.

8.4.4.1 Dose Modification Guidelines for Hematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/Rituximab)

Dose modifications guidelines for hematologic toxicities for Cohorts A and B are presented in Table 8.i.

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Table 8.i Dose Modification Guidelines for Hematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/Rituximab)

NCI CTCAE Grade	Description	Bendamustine Dose Modification Rituximab Dose Modification	TAK-659 Dose Modification
Neutropenia			
2 or 3	ANC <1500 to 500/mm^3; <1.5 to 0.5×10^9/L	Hold dose of bendamustine until ANC ≥1000/mm^3 or baseline, then restart at same schedule and dose (90 mg/m^2). Maintain rituximab at same dose and schedule (375 mg/m^2).	Continue TAK-659 at same dose and schedule.
4	ANC <500/mm^3; <0.5×10^9/L	Hold bendamustine dose until ANC ≥1000/mm^3 or baseline, then restart bendamustine dose at 90 mg/m^2. If resolved in ≤7 days, maintain the same dose of bendamustine. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence). Hold rituximab until ANC ≥1000/mm^3 or baseline, then restart rituximab dose at same dose and schedule (375 mg/m^2).	Hold TAK-659 until ANC ≥1000/mm^3 or baseline, then restart TAK-659 at same dose and schedule. In case of repeat occurrence at a reduced dose of bendamustine, TAK-659 may be reduced by 1 level (first occurrence) and by 2 levels if needed.
Other	Febrile neutropenia: ANC <1000/mm^3 and fever defined as a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour), OR ANC <1000/mm^3 with systemic infection	Hold bendamustine dose until ANC ≥1000/mm^3 or baseline and fever and infection are resolved, then restart bendamustine at dose reduced by 1 level (first occurrence) and by 2 levels (repeat occurrence). Hold rituximab until ANC ≥1000/mm^3 or baseline, then restart rituximab dose at same dose and schedule (375 mg/m^2).	Hold TAK-659 until ANC ≥1000/mm^3 or baseline, then restart TAK-659 at same dose and schedule. In case of repeat occurrence at a reduced dose of bendamustine, TAK-659 may be reduced by 1 level first and by 2 levels if needed.
Thrombocytopenia			
1 or 2	PLT < LLN to 50,000/mm^3; <LLN to 50×10^9/L	Hold bendamustine until PLT ≥75,000/mm^3 or baseline, then restart at the same dose. Maintain rituximab at same dose and schedule (375 mg/m^2).	No change. Continue TAK-659 at same dose and schedule.
3	PLT < 50,000-25,000/mm^3; <50 to 25×10^9/L	Hold bendamustine until PLT ≥75,000/mm^3 or baseline. If resolved in ≤7 days, maintain the same dose. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence). Hold rituximab until PLT ≥75,000/mm^3 or baseline, then restart rituximab at same dose and schedule (375 mg/m^2).	Hold TAK-659 until PLT ≥75,000/mm^3 or baseline, then restart TAK-659 at same dose and schedule.

Footnotes are on last table page.

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Table 8.i Dose Modification Guidelines for Hematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/ Rituximab) (continued)

NCI CTCAE Grade	Description	Bendamustine Dose Modification Rituximab Dose Modification	TAK-659 Dose Modification
4	PLT <25,000/mm^3; <25×10^9/L	Hold bendamustine until PLT ≥75,000/mm^3 or baseline. When resolved, reduce bendamustine dose by 1 level (first occurrence) and by 2 levels (repeat occurrence). Hold rituximab until PLT ≥75,000/mm^3 or baseline, then restart rituximab at same dose and schedule (375 mg/m^2).	Hold TAK-659 until PLT ≥75,000/mm^3 or baseline; restart TAK-659 at same dose. In case of recurrence at a reduced dose of bendamustine, TAK-659 may be reduced by 1 level first and by 2 levels if needed.
Other	PLT <10,000/mm^3 OR clinically significant bleeding	Consider permanently discontinuing bendamustine, except when the investigator determines that the patient is obtaining a clinical benefit and the investigator has discussed this with the sponsor. If bendamustine is not discontinued, then the bendamustine dose will be reduced to at least 1 dose level when PLT ≥75,000/mm^3 or baseline and/or clinically significant bleeding are completely resolved. Consider permanently discontinuing rituximab, except when the investigator determines that the patient is obtaining a clinical benefit and the investigator has discussed this with the sponsor. If rituximab is not discontinued, then maintain the starting dose and schedule (375 mg/m^2) when PLT ≥75,000/mm^3 or baseline and/or clinically significant bleeding are completely resolved.	Consider permanently discontinuing TAK-659, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient is not withdrawn from the study, the TAK-659 dose will be reduced to at least 1 dose level lower when PLT ≥75,000/mm^3 or baseline and/or clinically significant bleeding are completely resolved.
Anemia			
3	Hgb <8.0 g/dL; transfusion indicated	Hold bendamustine until Hgb ≥9.0 g/dL or baseline. If resolved in ≤7 days, maintain the same dose of bendamustine. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence). Hold rituximab until Hgb ≥9.0 g/dL or baseline. Restart rituximab dose at 375 mg/m^2. In case of repeat occurrence at a reduced dose of TAK-659, rituximab will be maintained at same dose and schedule (375 mg/m^2).	Hold TAK-659 until Hgb ≥9.0 g/d or baseline. If resolved in ≤7 days, maintain the same dose of TAK-659. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).
4	Life-threatening consequences; urgent intervention indicated	Hold bendamustine until resolved to Grade ≤1 or baseline. Restart at reduced dose by at least 1 level, or consider discontinuation. Hold rituximab until Hgb ≥9.0 g/dL or baseline. Restart rituximab dose at 375 mg/m^2.	Hold TAK-659 until Hgb ≥9.0 g/dL or baseline. When resolved, reduce dose by at least 1 level, or consider discontinuation.

Hgb: hemoglobin; PLT: platelets.

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8.4.4.2 Dose Modification Guidelines for Nonhematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/Rituximab)

Dose modifications guidelines for non-hematologic toxicities for Cohort A and Cohort B are presented in Table 8.j.

Table 8.j Dose Modification Guidelines for Nonhematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/ Rituximab)

NCI CTCAE Grade	Bendamustine Dose Modification Rituximab Dose Modification	TAK-659 Dose Modification
Asymptomatic Serum Lipase and/or Amylase Increase		
Asymptomatic lipase elevation (Grade <4) in the absence of significant amylase elevation (Grade <3) considered not dose limiting between sponsor and investigators.	Maintain the same dose/regimen of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Asymptomatic amylase elevation (Grade <4) in the absence of significant lipase elevation (Grade <3) considered not dose limiting between sponsor and investigators.	Maintain the same dose/regimen of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Asymptomatic Grade 3 serum lipase increase accompanied by Grade ≥3 serum amylase increase; asymptomatic Grade 3 serum amylase increase accompanied by Grade ≥3 serum lipase increase; OR asymptomatic Grade 4 serum lipase or amylase increase.	Maintain the same dose/regimen of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Hold TAK-659 until resolution to Grade ≤1, baseline, or a level acceptable by the investigator (must be Grade ≤2), then restart TAK-659 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days. If recurs, then reduce by 1 level.
AST/ALT		
Grade 3 elevation of single enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3)	Maintain the dose of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Grade 3 elevation of both AST and ALT	Hold bendamustine until AST and ALT decrease to <2.5 × ULN. Restart bendamustine at the same dose if resolved within 7 days or reduce by 1 level if resolution is >7 days. Hold rituximab until AST and ALT decrease to <2.5 × ULN, then restart rituximab at same dose and schedule (375 mg/m^2).	Hold TAK-659 until AST and ALT decrease to <2.5 × ULN. Restart TAK-659 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days.
Grade 4 elevation of AST and/or ALT	Hold bendamustine until AST and ALT <2.5 × ULN. Restart bendamustine at a dose reduced by 1 level, and if elevation recurs, reduce by 2 dose levels. Hold rituximab until AST and ALT decrease to <2.5 × ULN, then restart rituximab at same dose and schedule (375 mg/m^2).	Hold TAK-659 until AST and ALT <2.5 × ULN. Restart TAK-659 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days. If recurs, then dose reduce by 1 level.).

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Table 8.j Dose Modification Guidelines for Nonhematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/ Rituximab) (continued)

NCI CTCAE Grade	Bendamustine Dose Modification Rituximab Dose Modification	TAK-659 Dose Modification
Other Nonhematologic Toxicities		
All other Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to Grade ≤1 or baseline within 1 week with optimal antiemetics and antidiarrheals following standard of care. • Transient Grade 3 fatigue (lasting <1 week). • Grade 3 rash lasting ≤7 days with optimal treatment. • Asymptomatic lipase elevation (Grade <4) in the absence of significant amylase elevation (Grade <3). • Asymptomatic amylase elevation (Grade <4) in the absence of lipase elevation (Grade <3). • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3). • Grade 3 hypophosphatemia resolved to Grade ≤1 or baseline within 72 hours with phosphate repletion. • Any other Grade 3 nonhematologic toxicity that can be controlled to Grade ≤1 or baseline in 1 week with appropriate treatment.	Hold bendamustine if determined to be related to bendamustine until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurs, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation of bendamustine should be considered if the toxicities persist as Grade ≥3 for more than 21 days despite temporary disruption of study drug. Hold rituximab if determined to be related to rituximab until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2). When resolved, maintain rituximab dose and schedule. Permanent discontinuation of rituximab should be considered if the toxicities persist as Grade ≥3 for >21 days despite temporary disruption of study drug.	Hold TAK-659 if determined to be related to TAK-659 until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurred, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as Grade ≥3 for more than 21 days despite temporary interruption of study drug. For exceptions, maintain dose level.

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Table 8.j Dose Modification Guidelines for Nonhematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/ Rituximab) (continued)

NCI CTCAE Grade	Bendamustine Dose Modification Rituximab Dose Modification	TAK-659 Dose Modification
Grade 4 nonhematologic toxicities with the exception of an asymptomatic laboratory change that is considered clinically manageable.	Permanent discontinuation of bendamustine or rituximab should be considered based on causality, except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient's treatment is not discontinued, the combination agent dose (for bendamustine) will be reduced to at least 1 dose level lower when toxicity resolves to Grade ≤1, baseline, or a level acceptable by the investigator (must be Grade ≤2) or held (for rituximab) until toxicity resolves to Grade ≤1, baseline, or a level acceptable by the investigator (must be Grade ≤2)	Permanent discontinuation should be considered except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, TAK-659 dose will be reduced to at least 1 dose level lower when toxicity resolves to Grade ≤1 or baseline. For the asymptomatic laboratory change exceptions, hold TAK-659 until resolution to Grade ≤1 or baseline. • If resolved in ≤7 days, then maintain the dose level; • If resolved in >7 days, then reduce dose by 1 dose level; • If recurs, then reduce dose by 1 dose level.

Grade 4 nonhematologic toxicities 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 of the toxicity(ies) in question to Grade 1 or to baseline values. When a dose reduction of TAK-659 is required because of Grade 4 nonhematologic toxicities, no re-escalation of dose will be permitted. For Grade 4 asymptomatic laboratory abnormalities (eg, lipase, amylase, AST, ALT, or CPK), TAK-659 should be held until resolution to Grade ≤1 or baseline. 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.

8.4.4.3 Dose Modification Guidelines for Hematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib)

Dose modifications guidelines for hematologic toxicities for Cohorts C, D, and E are presented in Table 8.k.

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Table 8.k Dose Modification Guidelines for Hematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib)

NCI CTCAE Grade	Description	Combination Drug Dose Modification (Gemcitabine, Lenalidomide, or Ibrutinib)	TAK-659 Dose Modification
Neutropenia			
2 or 3	ANC <1500 to 500/mm^3; <1.5 to 0.5×10^9/L	Hold dose of combination agent until ANC ≥1000/mm^3 or baseline, then restart at same schedule and dose.	Continue TAK-659 at same dose and schedule.
4	ANC <500/mm^3; <0.5×10^9/L	Hold combination agent dose until ANC ≥1000/mm^3 or baseline, then restart combination agent. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until ANC ≥1000/mm^3 or baseline, then restart TAK-659 at same dose and schedule. In case of repeat occurrence at a reduced dose of the combination agent, TAK-659 may be reduced by 1 level (first occurrence) and by 2 levels if needed.
Other	Febrile neutropenia: ANC <1000/mm^3 and fever defined as a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour), OR ANC <1000/mm^3 with systemic infection	Hold combination agent dose until ANC ≥1000/mm^3 or baseline and fever and infection are resolved, then restart combination agent at dose reduced by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until ANC ≥1000/mm^3 or baseline, then restart TAK-659 at same dose and schedule. In case of repeat occurrence at a reduced dose of combination agent, TAK-659 may be reduced by 1 level first and by 2 levels if needed.
Thrombocytopenia			
1 or 2	PLT < LLN to 50,000/mm^3; <LLN to 50×10^9/L	Hold combination agent until PLT ≥75,000/mm^3 or baseline, then restart at the same dose.	No change. Continue TAK-659 at same dose and schedule.
3	PLT <50,000 to 25,000/mm^3; <50 to 25×10^9/L	Hold combination agent until PLT ≥75,000/mm^3 or baseline. If resolved in ≤7 days, maintain the same dose. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until PLT ≥75,000/mm^3 or baseline, then restart TAK-659 at same dose and schedule.
4	PLT <25,000/mm^3; <25×10^9/L	Hold combination agent until PLT ≥75,000/mm^3 or baseline. When resolved, reduce combination agent dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until PLT ≥75,000/mm^3 or baseline, then restart TAK-659 at same dose. In case of recurrence at a reduced dose of combination agent, TAK-659 may be reduced by 1 level first and by 2 levels if needed.

Footnotes are on last table page.

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Table 8.k Dose Modification Guidelines for Hematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib) (continued)

NCI CTCAE Grade	Description	Combination Drug Dose Modification (Gemcitabine, Lenalidomide, or Ibrutinib)	TAK-659 Dose Modification
Other	PLT <10,000/mm^3; OR clinically significant bleeding	Consider permanently discontinuing combination agent, except when the investigator determines that the patient is obtaining a clinical benefit, and the investigator has discussed this with the sponsor. If combination agent is not discontinued, then the combination agent dose will be reduced by at least 1 dose level when PLT ≥75,000/mm^3 or baseline and/or clinically significant bleeding are completely resolved.	Consider permanently discontinuing TAK-659, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor. If the patient is not withdrawn from the study, the TAK-659 dose will be reduced by at least 1 dose level when PLT ≥75,000/mm^3 or baseline and/or clinically significant bleeding are completely resolved.
Anemia			
3	Hgb <8.0 g/dL; transfusion indicated	Hold combination agent until Hgb ≥9.0 g/dL or baseline. If resolved in ≤7 days, maintain the same dose of combination agent. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).	Hold TAK-659 until Hgb ≥9.0 g/dL or baseline. If resolved in ≤7 days, maintain the same dose of TAK-659. If resolved in >7 days, reduce dose by 1 level (first occurrence) and by 2 levels (repeat occurrence).
4	Life-threatening consequences; urgent intervention indicated	Hold combination agent until resolved to Grade ≤1 or baseline. Restart combination agent at a dose reduced by at least 1 level or consider discontinuation.	Hold TAK-659 until Hgb ≥9.0 g/dL or baseline. When resolved, reduce dose by at least 1 level, or consider discontinuation.

Hgb: hemoglobin; PLT: platelets.

8.4.4.4 Dose Modification Guidelines for Nonhematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib)

Dose modifications guidelines for nonhematologic toxicities for Cohorts C, D, and E are presented in Table 8.l.

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Table 8.l Dose Modification Guidelines for Nonhematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib)

NCI CTCAE Grade	Combination Drug Dose Modification (Gemcitabine, Lenalidomide, or Ibrutinib)	TAK-659 Dose Modification
Asymptomatic Serum Lipase and/or Amylase Increase		
Asymptomatic lipase elevation (Grade <4) in the absence of significant amylase elevation (Grade <3) considered not dose limiting between sponsor and investigators.	Maintain the same dose/regimen of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Asymptomatic amylase elevation (Grade <4) in the absence of significant lipase elevation (Grade <3) considered not dose limiting between sponsor and investigators.	Maintain the same dose/regimen of bendamustine with close monitoring. Maintain rituximab at same dose and schedule with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Asymptomatic Grade 3 serum lipase increase accompanied by Grade ≥3 serum amylase increase; asymptomatic Grade 3 serum amylase increase accompanied by Grade ≥3 serum lipase increase; OR asymptomatic Grade 4 serum lipase or amylase increase.	Maintain the same dose/regimen of combination agent with close monitoring.	Hold TAK-659 until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2), then restart TAK-659 at the same dose if resolved within 7 days, or reduce by 1 level if resolution is more than 7 days. If recurs, then reduce by 1 dose level.
AST/ALT		
Grade 3 elevation of single enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3)	Maintain the dose of combination agent with close monitoring.	Maintain the dose of TAK-659 with close monitoring.
Grade 3 elevation of both AST and ALT	Hold combination agent until AST and ALT decrease to <2.5 × ULN. Restart combination agent at the same dose if resolved within 7 days, or reduce by 1 level if resolution is >7 days.	Hold TAK-659 until AST and ALT decrease to <2.5 × ULN. Restart TAK-659 at the same dose if resolved within 7 days or reduce by 1 level if resolution is more than 7 days.
Grade 4 elevation of AST and/or ALT	Hold combination agent until AST and ALT <2.5 × ULN. Restart combination agent at a reduced dose by 1 level; if elevation recurs, reduce by 2 dose levels.	Hold TAK-659 until AST and ALT <2.5 × ULN. Restart TAK-659 at the same dose if resolved within 7 days, or reduce by 1 level if resolution is more than 7 days. If recurs, then reduce dose by 1 level.

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Table 8.l Dose Modification Guidelines for Nonhematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib) (continued)

NCI CTCAE Grade	Combination Drug Dose Modification (Gemcitabine, Lenalidomide, or Ibrutinib)	TAK-659 Dose Modification
Other Nonhematologic Toxicities		
All other Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to Grade ≤1 or baseline within 1 week with optimal antiemetics and antidiarrheals following SOC. • Transient Grade 3 fatigue (lasting <1 week). • Grade 3 rash lasting ≤7 days with optimal treatment. • Asymptomatic lipase elevation (Grade <4) in the absence of significant amylase elevation (Grade <3). • Asymptomatic amylase elevation (Grade <4) in the absence of lipase elevation (Grade <3). • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3). • Grade 3 hypophosphatemia resolved to Grade ≤1 or baseline within 72 hours with phosphate repletion. • Any other Grade 3 nonhematologic toxicity that can be controlled to Grade ≤1 or baseline in 1 week with appropriate treatment.	Hold combination agent if determined to be related to combination agent until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurs, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as Grade ≥3 for more than 21 days despite temporary interruption of study drug.	Hold TAK-659 if determined to be related to TAK-659 until resolution to Grade ≤1, baseline, or a level acceptable to the investigator (must be Grade ≤2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurred, then reduce dose by 1 dose level. • For the exceptions listed, maintain the dose level. Permanent discontinuation should be considered if the toxicities persist as Grade ≥3 for more than 21 days despite temporary interruption of study drug. For exceptions, maintain dose level.

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Table 8.l Dose Modification Guidelines for Nonhematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib) (continued)

NCI CTCAE Grade	Combination Drug Dose Modification (Gemcitabine, Lenalidomide, or Ibrutinib)	TAK-659 Dose Modification
Grade 4 nonhematologic toxicities with the exception of an asymptomatic laboratory change that is considered clinically manageable.	Permanent discontinuation of combination agent should be considered based on causality, except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient's treatment is not discontinued, the combination agent dose will be reduced to at least 1 dose level lower when toxicity resolves to Grade ≤1, baseline, or a level acceptable by the investigator (must be Grade ≤2).	Permanent discontinuation should be considered based on causality except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient's treatment is not discontinued, TAK-659 dose will be reduced to at least 1 dose level lower when toxicity resolves to Grade ≤1 or baseline. For the asymptomatic laboratory change exceptions, hold TAK-659 until resolution to Grade ≤1 or baseline. If resolved in ≤7 days, then maintain the dose level; If resolved in >7 days, then reduce dose by 1 dose level; If recurs, then reduce dose by 1 dose level.

Grade 4 nonhematologic toxicities 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 of the toxicity or toxicities in question to Grade 1 or to baseline values. When a dose reduction of TAK-659 is required due to Grade 4 nonhematologic toxicities, no re-escalation of dose will be permitted. For Grade 4 asymptomatic laboratory abnormalities (eg, lipase, amylase, AST, ALT, or CPK), TAK-659 should be held until resolution to Grade ≤1 or baseline. 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.

8.5 Excluded 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 taking or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

The following restrictions apply during the study:

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a) Any antineoplastic therapy other than TAK-659 and its combination study drug(s) 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 eCRF.

b) Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD) is not permitted during the study. Palliative radiotherapy for local pain/symptom control in a preexisting nontarget lesion, if required, may be considered after discussion with the sponsor's clinical representative. Details of the palliative radiotherapy should be documented in the source records and eCRF, including dates of treatment, anatomical site, dose administered and fractionation schedule, and associated AEs.

c) 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 and as outlined in Section 8.6). Tropical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) are allowed.

d) 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. Patients who experience severe and/or febrile neutropenia during the study can be managed with growth factor support if needed, including prophylactic use of growth factor, in accordance with American Society of Clinical Oncology (ASCO) guidelines.

e) 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 for a 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.

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

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

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

8.5.1 Excluded Concomitant Medications Applicable to Cohorts A and B

Cohorts A and B (TAK-659 + bendamustine ±rituximab): Please refer to the most recent bendamustine and rituximab USPI [11,12], Bendeka USPI [17], or applicable labeling for information on medications that are prohibited in patients receiving bendamustine ±rituximab.

8.5.2 Excluded Concomitant Medications Applicable to Cohort C

Cohort C (TAK-659 + gemcitabine): Please refer to the most recent gemcitabine USPI [13] or applicable labeling for information on medications that are prohibited in patients receiving gemcitabine.

8.5.3 Excluded Concomitant Medications Applicable to Cohort D

Cohort D (TAK-659 + lenalidomide): Please refer to the most recent lenalidomide USPI [15] or applicable labeling for information on medications that are prohibited in patients receiving lenalidomide.

8.5.4 Excluded Concomitant Medications Applicable to Cohort E

Cohort E (TAK-659 + ibrutinib): Please refer to the most recent ibrutinib USPI [16] or applicable labeling for information on medications that are prohibited in patients receiving ibrutinib.

For patients in the ibrutinib combination arm (Cohort E), concurrent systemic treatment with moderate inhibitors or inducers of CYP3A is also not permitted in this study because of the

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potential risk for clinically relevant DDI with ibrutinib. Refer to the list below and Appendix H for a list of medications, supplements, and food products that are moderate inhibitors or inducers of CYP3A based on the US Food and Drug Administration (FDA) Draft DDI Guidance.

- Antibiotics: ciprofloxacin, nafcillin.
- Antiemetic: aprepitant.
- Antifungal: fluconazole.
- Endothelin receptor antagonist: bosentan.
- Food/beverages: Seville oranges (often contained in marmalades).
- Stimulant: modafinil.

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

  If a patient experiences an AE on study and combination drug dosing is temporarily interrupted due to that AE, the medications listed above may be used for AE management provided there is no appropriate alternative treatment available based on the investigator's judgement and the dosing is not concurrent with the combination drug. This situation requires discussion between the investigator and the medical monitor, and the discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

8.6 Permitted Concomitant Medications and Procedures

8.6.1 Rituximab Premedication for Cohort B

For patients in Cohort B receiving rituximab, premedicate with acetaminophen and an antihistamine before rituximab infusion in accordance with the rituximab USPI [12] or applicable labeling. Appropriate institutional practices consistent with the rituximab label and recommendations should be followed.

8.6.2 Additional Concomitant Medications and Procedures

- Additional concomitant medications and procedures are permitted during the course of the study (please refer to Section 8.8) to prevent and actively manage AEs related or not related to the study drug(s) unless otherwise specified in Section 8.5.

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8.7 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.

For patients in the bendamustine or bendamustine + rituximab combination arms (Cohorts A and B), caution should be used or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed (see Appendix H).

It is not known what effects TAK-659 has on human pregnancy or development of the embryo or fetus when administered in combination with bendamustine, rituximab, gemcitabine, lenalidomide, or ibrutinib; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception throughout defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix F) at the same time, from the time of signing of the ICF through 180 days after the last dose of study drug (or 12 months after the last dose of study drug for patients in the rituximab combination arm), or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Female patients should not donate ova from the time of signing the informed consent through 180 days after the last dose of study drug.

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

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug (or 12 months after the last dose of study drug for patients in the rituximab combination arm), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation

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methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- For both men and women in the rituximab combination arm (Cohort B): patients must practice contraception as described above from the time of signing of the ICF through 12 months after the last dose of study drug.
- For both men and women in the lenalidomide combination arm (Cohort D): patients must adhere to the guidelines of the RevAssist program (US participants) or the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the study manual (all other participants who are not using commercial supplies). For additional precautions and restrictions for each of the combination arms, please see the applicable USPIs [11-13,15-17] or applicable labeling.

8.8 Management of TAK-659–Related Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on 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 dose escalation. The combination drugs are associated with various AEs, which may be managed per clinical judgment of the investigator in accordance with the institutional guideline and the most recent USPI [11-13,15-17] or applicable labeling for each drug. Additional treatment algorithms for use in conjunction with clinical judgment are provided below. If dose modification of study drug(s) is necessary as a result of the events detailed below, please refer to Section 8.4.

8.8.1 Prophylaxis Against Infection

Patients with advanced hematologic malignancies may be at an increased risk of infection. Prophylactic use of antibiotic, antiviral, or antifungal medication can be considered as clinically indicated and per local standard practice or per National Comprehensive Cancer Network Prevention and Treatment of Cancer-Related Infections Guidelines. In particular, lymphopenia can develop in association with either treatment or with the underlying disease (lymphoma). Lymphopenia can be associated with reactivation of herpes zoster, CMV, herpes simplex, and other viruses. Antiviral therapy, such as acyclovir, ganciclovir, valacyclovir, or other antiviral agents, may be initiated as clinically indicated. It is recommended that prophylaxis for varicella-zoster virus should be administered for Cohort B [19].

Given their degree of immunosuppression, subjects with posttransplant lymphoproliferative disease are often at an increased risk of developing infections. Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the subject is more prone to developing neutropenia. Subjects who develop neutropenic fever should be evaluated promptly and treated immediately with parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.

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8.8.1.1 CMV Monitoring and Prophylaxis

At screening, on Day 1 of each treatment cycle, and at end of treatment (EOT), all subjects should have CMV serology and/or quantitative polymerase chain reaction (PCR) assay performed. If positive at any timepoint, CMV monitoring is advised once a week with a decrease to once every cycle as it becomes negative. Interruption of study drug is generally advised if the positive CMV test is accompanied by associated clinical symptoms, if the copy number reaches a level indicates a need for treatment per institutional standard, or if the CMV test remains positive despite the antiviral treatment for CMV. Further monitoring and prophylactic or preemptive therapy for asymptomatic patients, if indicated, should follow the institutional standard practice. The following agents should be considered for prophylaxis or pre-emptive treatment against CMV: ganciclovir (IV), valganciclovir (PO), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until CMV is no longer detected per PCR.

8.8.1.2 Prophylaxis for Opportunistic Infections

Patients with lymphopenia may also be more prone to developing infections, such as respiratory tract infections or pneumonia. Consider a diagnosis of opportunistic infection, including PJP, in patients presenting with shortness of breath, cough, or fever.

Prophylaxis for PJP must be initiated (either at baseline or during treatment) if the following is present:

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

It is recommended that the prophylaxis for PJP should be implemented in Cohort B regardless of the above-mentioned conditions [19]. For older patients; patients with recent exposure to steroids, rituximab, cyclophosphamide, or immunosuppressive agents; or patients who, in the investigator's opinion, are more susceptible to opportunistic infection at baseline, PJP prophylaxis should be considered at the start of study treatment. When steroids or any immunomodulatory agents need to be used to manage AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is coadministered. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated; however, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

8.8.2 Pneumonitis

Patients with serious lung events who 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 be advised to promptly report respiratory symptoms.

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8.8.3 Nausea and/or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation, unless part of the local standard of care for administration of a combination agent (eg, bendamustine, gemcitabine). However, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules.

8.8.4 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 per the dose modification guidelines in Table 8.j and Table 8.l.

8.8.5 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 in the event of Grade 3 or 4 rash. Refer to dose modification guidelines in Table 8.j and Table 8.l.

8.8.6 Diarrhea

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

8.8.7 Anemia, Thrombocytopenia, and/or Neutropenia

Hemoglobin and blood counts should be monitored regularly as outlined in Appendix A, with additional testing obtained according to standard clinical practice. Administration of TAK-659 and combination drugs should be modified per dose modification guidance in the protocol when anemia, thrombocytopenia, or neutropenia occur (see Table 8.i and Table 8.k). RBC transfusion and use of erythropoietin to manage severe anemia, platelet transfusion to prevent and minimize bleeding in case of severe thrombocytopenia, and myeloid growth factor (eg, G-CSF, GM-CSF) support to treat severe and/or febrile neutropenia are permitted per ASH/ASCO guidelines, as necessary. However, it should be noted that prophylactic use of myeloid growth factors should be avoided during the first cycle of dose escalation (see Section 8.5).

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8.8.8 Hypophosphatemia

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

8.8.9 Enzyme Elevations

8.8.9.1 Transaminase, Amylase and Lipase, and CPK Elevations

Elevations of the enzymes above have been observed. Events are generally asymptomatic and reversible with dose interruption. See dose modification guidelines in Table 8.j.

8.8.9.2 LDH Elevations

LDH elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic, and their clinical significance is unknown. No doses have been interrupted because of increased LDH; however, LDH elevations have been observed to be reversible in patients who had TAK-659 interrupted for other reasons.

8.8.10 Fluid Deficit

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

8.9 Management of Combination Drug-Related Clinical Events

Clinical characteristics and risk mitigation measures addressing each of the important combination drug–related clinical events are summarized below. Refer to the most recent USPI [11-13,15-17] or applicable labeling for each drug for further details.

8.9.1 Infusion Reactions

Severe infusion reactions have been reported in clinical trials of bendamustine and rituximab and can manifest with a variety of symptoms, including fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, and others. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4.03 guidelines [1]. Treatment recommendations for all infusion reactions from bendamustine and rituximab in accordance with USPI [12] or applicable labeling guidelines are provided below and may be modified based on local treatment standards and guidelines as clinically appropriate.

Infusion reaction symptoms for bendamustine include fever, chills, pruritus, and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics, and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue bendamustine for patients with Grade 4 infusion reactions.

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Consider discontinuation for Grade 3 infusion reactions as clinically appropriate considering individual benefits, risks, and supportive care.

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion with a time to onset of 30 to 120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, and death. Premedicate patients with an antihistamine and acetaminophen before dosing. Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm).

8.9.2 Cohorts A and B (Bendamustine-Related) Clinical Events

Please refer to the most recent Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling for more information on bendamustine-related clinical events, such as severe skin reactions, extravasation injury, etc, and for the management of clinical events in patients receiving bendamustine.

8.9.3 Cohort B (Rituximab-Related) Clinical Events

Please refer to the most recent rituximab USPI [12] or applicable labeling for more information on rituximab-related clinical events, such as severe mucocutaneous reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, etc, and for the management of clinical events in patients receiving rituximab.

8.9.4 Cohort C (Gemcitabine-Related) Clinical Events

Please refer to the most recent gemcitabine USPI [13] or applicable labeling for more information on gemcitabine-related clinical events, such as unexplained dyspnea or other evidence of severe pulmonary toxicity, hemolytic-uremic syndrome, capillary leak syndrome, etc, and for the management of clinical events in patients receiving gemcitabine.

8.9.5 Cohort D (Lenalidomide-Related) Clinical Events

Please refer to the most recent lenalidomide USPI [15] or applicable labeling for more information on lenalidomide-related clinical events, such as venous and arterial thromboembolic events, tumor flare reactions, etc, and for the management of clinical events in patients receiving lenalidomide.

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8.9.6 Cohort E (Ibrutinib-Related) Clinical Events

Please refer to the most recent ibrutinib USPI [16] or applicable labeling for ibrutinib-related clinical events such as hemorrhage, infections, cytopenias, atrial fibrillation, tumor lysis syndrome, etc, and for the management of clinical events in patients receiving ibrutinib.

8.10 Blinding and Unblinding

This is an open-label study.

8.11 Description of Investigational Agents

8.11.1 Description of TAK-659

TAK-659 has been formulated into immediate-release, film-coated tablets for use in phase 1 clinical studies via a common granulation process. Three different tablet dosage strengths, 20, 60, and 100 mg, were formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets were coated with Opadry film coat.

8.11.2 Description of Bendamustine

Bendamustine is a commercially available drug and will be procured or distributed according to the pharmacy manual. Bendamustine is supplied as 100 mg/4 mL (25 mg/mL) in a multiple-dose vial or 100 mg lyophilized powder in a 20 mL single-dose vial for reconstitution. Only 1 formulation should be used for each patient, and the formulation used should be consistent with local practice guidelines. Please refer to the most recent Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling.

8.11.3 Description of Rituximab

Rituximab is a commercially available drug and will be procured or distributed according to the pharmacy manual. Rituximab is provided as 100 mg/10 mL or 500 mg/50 mL solution for injection in a single-dose vial. Please refer to the most recent rituximab USPI [12] or applicable labeling.

8.11.4 Description of Gemcitabine

Gemcitabine is a commercially available drug and will be procured or distributed according to the pharmacy manual. Gemcitabine is provided as 200 mg lyophilized powder in a 10 mL single-use vial or 1 g lyophilized powder in a 50 mL single-use vial for injection. Please refer to the most recent gemcitabine USPI [13] or applicable labeling.

8.11.5 Description of Lenalidomide

Lenalidomide is a commercially available drug supplied as 25 mg capsules and will be procured or distributed according to the pharmacy manual. Please refer to the most recent lenalidomide USPI [15] or applicable labeling.

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8.11.6 Description of Ibrutinib

Ibrutinib is a commercially available drug supplied as 140 mg capsules and will be procured or distributed according to the pharmacy manual. Please refer to the most recent ibrutinib USPI [16] or applicable labeling.

8.12 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

8.12.1 TAK-659 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing TAK-659 immediate-, 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.

8.12.2 Bendamustine Preparation, Reconstitution, and Dispensation

Bendamustine is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the pharmacy manual. Please refer to the most recent Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling.

8.12.3 Rituximab Preparation, Reconstitution, and Dispensation

Rituximab is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the pharmacy manual. Please refer to the most recent rituximab USPI [12] or applicable labeling.

8.12.4 Gemcitabine Preparation, Reconstitution, and Dispensation

Gemcitabine is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the pharmacy manual. Please refer to the most recent gemcitabine USPI [13] or applicable labeling.

8.12.5 Lenalidomide Preparation, Reconstitution, and Dispensation

Lenalidomide is a commercially available drug supplied as 25 mg capsules and will be procured or distributed according to the pharmacy manual. Please refer to the most recent lenalidomide USPI [15] or applicable labeling.

8.12.6 Ibrutinib Preparation, Reconstitution, and Dispensation

Ibrutinib is a commercially available drug supplied as 140 mg capsules and will be procured or distributed according to the pharmacy manual. Please refer to the most recent ibrutinib USPI [16] or applicable labeling.

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8.13 Packaging and Labeling

8.13.1 TAK-659 Packaging and Labeling

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

8.13.2 Bendamustine Packaging and Labeling

Bendamustine will be supplied to the site from commercial sources. Please refer to the most recent Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling.

8.13.3 Rituximab Packaging and Labeling

Rituximab will be supplied to the site from commercial sources. Please refer to the most recent rituximab USPI [12] or applicable labeling.

8.13.4 Gemcitabine Packaging and Labeling

Gemcitabine will be supplied to the site from commercial sources. Please refer to the most recent gemcitabine USPI [13] or applicable labeling.

8.13.5 Lenalidomide Packaging and Labeling

Lenalidomide will be supplied to the site from commercial sources. Please refer to the most recent lenalidomide USPI [15] or applicable labeling.

8.13.6 Ibrutinib Packaging and Labeling

Ibrutinib will be supplied to the site from commercial sources. Please refer to the most recent ibrutinib USPI [16] or applicable labeling.

8.14 Storage, Handling, and Accountability

8.14.1 TAK-659 Storage, Handling, and Accountability

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

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

Because TAK-659 is an investigational agent, it should be handled with due care. In the case of broken tablets, raising dust should be avoided during the clean-up operation. Damaged tablets may be harmful by inhalation, ingestion, or skin and/or eye contact. In the case of contact of damaged tablets with the eyes or skin, there should be immediate and thorough flushing and washing 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 TAK-659 dosing compliance. Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

8.14.2 Bendamustine Storage, Handling, and Accountability

Bendamustine should be stored according to instructions provided in the manufacturer's Treanda USPI [11], Bendeka USPI [17], or applicable local bendamustine labeling.

8.14.3 Rituximab Storage, Handling, and Accountability

Rituximab should be stored according to instructions provided in the manufacturer's USPI [12] or applicable labeling.

8.14.4 Gemcitabine Storage, Handling, and Accountability

Gemcitabine should be stored according to instructions provided in the manufacturer's USPI [13] or applicable labeling.

8.14.5 Lenalidomide Storage, Handling, and Accountability

Lenalidomide should be stored according to instructions provided in the manufacturer's USPI [15] or applicable labeling.

8.14.6 Ibrutinib Storage, Handling, and Accountability

Ibrutinib should be stored according to instructions provided in the manufacturer's USPI [16] or applicable labeling.

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

For 24-hour contact information, refer to the study manual.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrolment 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).

9.3 Treatment Group Assignments

This is a phase 1, dose escalation study. Patients will be assigned to a dose cohort based on the dose escalation rules described in Section 8.3.

9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, and end of treatment (EOT). 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. The timing of PK and pharmacodynamic assessments is specified in the Schedule of Events Appendix A, Table 3 and Table 4) and is not flexible. Laboratory assessments and procedures may occur up to 3 days before the scheduled day due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).

Refer to the Schedule of Events (Appendix A) for the timing of assessments for 21-Day cycles (Cohorts A, B, and C; Appendix A, Table 1) and for 28-Day cycles (Cohorts D and E; Appendix A, Table 2). 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.

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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 and include a description of prior therapies for it. 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, Table 1 and Table 2). Complete physical examinations will be performed at screening, Day 1 of each cycle of treatment, and EOT. Symptom- or finding-directed physical examinations will be performed at all other visits specified in the Schedule of Events (Appendix A, Table 1 and Table 2).

9.4.5 Patient Height

Height will be measured only during screening (within 28 days before the first dose of study drug).

Weight will be measured during the times specified in the Schedule of Events (Appendix A, Table 1 and Table 2).

9.4.6 Vital Signs

Vital sign measurements include diastolic and systolic blood pressure, heart rate, temperature, and oxygen saturation, and will be assessed as specified in the Schedule of Events (Appendix A, Table 1 and Table 2). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for approximately 5 minutes.

9.4.7 ECOG Performance Status

ECOG performance status is to be assessed at the times specified in the Schedule of Events (Appendix A, Table 1 and Table 2).

9.4.8 ECG

A 12-lead, singlet ECG will be performed and interpreted locally at the time points specified in the Schedule of Events (Appendix A, Table 1 and Table 2).

All scheduled ECGs should be performed predose, unless otherwise specified in Appendix A, Table 3 and Table 4 for Cycle 1, and after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the

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timing of ECG measurements, the ECG will be completed before the collection of the blood sample. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

Confirmation that the machine-estimates of the rate-corrected QT interval (milliseconds) of electrocardiograph (QTc) are accurate using the appropriate QT correction formula (QTcF, Bazett's corrected QT interval) should be performed. Estimates of QTc for study eligibility should use QTcF. If a QTcF value confirmed by a qualified reader is >475 msec for a woman or >450 msec for a man, an evaluation to determine etiology should be conducted. If the prolonged QTc finding can be corrected by changing medication and/or correcting 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 or >60 msec elevated from baseline for any ECG, the following will occur:

a) The sponsor's clinician will be promptly notified.

b) Study treatment should be held, and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).

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

The decision to reinitiate study treatment with or without dose reduction (dose reduction applicable to TAK-659 only) and additional monitoring in those patients who had asymptomatic prolonged QTc >500 msec or >60 msec from baseline (Grade 3) that has reverted to an acceptable interval, have previously tolerated study treatment, and appear to have benefited from study treatment with either disease control or response must be agreed upon by the investigator and the sponsor's clinician on a case-by-case basis.

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

9.4.9 Concomitant Medications and Procedures

Concomitant medications and procedures 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 a list of excluded concomitant medications and procedures to be avoided during the study unless otherwise specified.

Concomitant medications and procedures 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 and Section for a list of excluded concomitant medications and procedures.

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AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A, Table 1 and Table 2). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.10 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.

9.4.11 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples are outlined in the study and laboratory manuals. Clinical laboratory evaluations will be performed as outlined below:

9.4.11.1 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 1 and Table 2).

Table 9.a Clinical Chemistry and Hematology Tests

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

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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 as follows (see also Appendix E):

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

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

9.4.12 Pregnancy Test

A serum pregnancy test will be performed for WOCBP at screening. For WOCBP, 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 is administered for that cycle. If a serum pregnancy test is performed within 3 days before dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1. For WOCBP, a urine pregnancy test also will be performed at EOT.

- For men and women both in Cohort D (TAK-659 + lenalidomide), patients must adhere to the guidelines of the RevAssist program (US participants) or the Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the study manual (all other participants who are not using commercial supplies). For additional precautions and restrictions for each of the combination arms, please see the applicable USPIs [11-13,15-17] or applicable labeling.

9.4.13 Ophthalmic Exam

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

9.4.14 Disease Assessment

Patients will undergo radiographic evaluation and symptom assessment to monitor and assess disease response. Response assessment will follow revised response criteria for malignant lymphoma per IWG 2007 criteria [2]. CT scans (with contrast) of the neck (if appropriate), chest,

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abdomen, and pelvis will be performed at screening/baseline (within 28 days before the first study drug administration), at the end of every other cycle through Cycle 6 and at the end of every 3 cycles thereafter (until PD or the start of alternative therapies), and at the EOT visit. For patients with FL or MZL in the Cohort B expansion phase, response will continue to be assessed during 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 baseline. 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 do not need to be conducted 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 unless contraindicated. 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 (Sézary cells).

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 an AE or other circumstances. If at the time of response assessment, a patient shows metabolic changes by PET (ie, increased or new FDG uptake) that are not consistent with lesion changes indicative of progression 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 is performed at the end of that cycle. If the metabolic changes by PET (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 by PET resolve and there is no indication of PD by CT or other, then the patient may remain on study; and 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 then required, and rebiopsy to confirm CR is also needed.

9.4.15 CT Scans

CT scans of the chest, abdomen, and pelvis (neck should be included if appropriate) will be performed to assess disease at screening and per the assessment schedule noted above and in the Schedule of Events (Appendix A, Table 1 and Table 2). All CT scans should be performed with IV contrast, and abdominal and pelvic CT scans should also be performed with oral contrast unless contraindicated. Hybrid PET-CT scanners may be used to acquire the required CT images only if CT produced by the scanner is of diagnostic quality, adheres to specified scan parameters, and includes IV contrast (unless medically contraindicated). Nondiagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only CT scan for the time

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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 is performed before the CT with IV contrast to avoid compromising the PET results.

9.4.16 PET Scans

A PET scan with FDG extending from the neck through the mid thighs will be performed to assess baseline disease at screening and to assess disease response at the end of Cycle 2 and Cycle 4. Examinations should be consistent across all time points, including amount of tracer, location of injection, arm position, and scan delay. If, however, the screening FDG-PET scan is negative, FDG-PET scans need not be performed at Cycles 2 and 4. After Cycle 4, PET scans will be performed only if needed to follow the disease, confirm the CR or PD status, or as indicated clinically. PET scans will be interpreted locally; central review of radiology will not be performed in this study. Note that if a patient achieves CR, PET scans are not required at subsequent assessments. The peak standardized uptake value (SUV) will be determined within the most FDG-avid metastases by the local nuclear medicine physician after initial qualitative assessment of the baseline PET scan and correlation with CT scan to confirm metastasis. Site-specific SUV will be accepted, and the highest SUV will be recorded.

9.4.17 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 identified on 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 end of study (optional to patients) if the initial biopsy was positive and a response has been achieved but relapse subsequently documented.

All scans and bone marrow test results will be interpreted locally. When possible, the same qualified physicians will interpret results to reduce variability. 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 for other cohorts. Test results and physician findings will be filed in patient source documents. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction. Objective response data collected for the CSR will be based on investigator assessment.

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[redacted]

9.4.21 PK Measurements

The primary aim of PK sampling in this study is to measure the plasma concentrations of TAK-659. However, pending technical feasibility, plasma samples for TAK-659 PK assessments may additionally be used for exploratory identification and profiling of TAK-659 metabolites to increase understanding of TAK-659 metabolism and clearance. If technically feasible, these plasma samples also could be used for exploratory measurement of bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib concentrations if considered appropriate based on emerging study findings (eg, if the incidence and severity of toxicity observed with combination drug is higher than anticipated).

Details on the collection, storage, processing, handling, and shipping of the PK samples are provided in the laboratory manual.

Blood samples for determination of TAK-659 plasma concentrations in the dose escalation and safety expansion phases will be obtained at the times indicated in Appendix A, Table 3 and Table 4. PK samples will be collected at prespecified time points relative to the dosing time of TAK-659. For example, the 24-hour postdose PK sample should be collected 24 hours (±1 hour) after the TAK-659 dose, not 24 hours after the combination drug dose. The samples obtained on Days 2 and 16 (approximately 24 hours after the Day 1 and 15 doses, respectively) should be obtained before TAK-659 dosing on those days. The predose samples on Day 8 and Day 15 also should be obtained before TAK-659 dosing on those days. On days with predose samples (or 24 hours postdose from the previous samples), patients should be instructed to refrain from taking their doses of TAK-659 (and lenalidomide and ibrutinib) at home before the clinic visit.

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[redacted]

9.4.23 CMV Testing

A blood sample will be obtained during screening, **on Day 1 of each cycle, and at the EOT visit,** as indicated in the Schedule of Events (Appendix A, Table 1 and Table 2) for the determination of CMV replication. The local CMV viral load data will be entered into the eCRF along with the normal range for the local assay. Further monitoring and prophylaxis or preemptive treatment against CMV in asymptomatic patients, if indicated, will follow the local standard practice.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed the study treatment when they have discontinued treatment with TAK-659.

9.6 Discontinuation of Treatment With Study Drug

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

- AE, including patients who experience a DLT (during escalation) during the first cycle, patients with Grade 4 nonhematologic toxicity, patients with Grade 4 anemia, and patients with other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.4 and the USPIs [11-13,15-17] or applicable labeling for the combination drugs. Discontinuation of treatment occurs only when both study drugs are required to be discontinued due to AEs.
- Protocol deviations.
- PD.
- Occurrence of pregnancy (if applicable).
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant
- Withdrawal of consent by patient.

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- In the opinion of the investigator, continued use of study drug is no longer in the patient's best interests.
- Lost to follow-up.
- Study terminated by sponsor.
- Other.

During the dose escalation phase, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

In the event of pregnancy, female subjects must discontinue use of study drugs. 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, Table 1 and Table 2). The primary reason for study drug discontinuation will be recorded on the eCRF.

9.7 Withdrawal of Patients From Study

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

- AE.
- Protocol deviation.
- Due to pregnancy.
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal of consent by patient.
- In the opinion of the investigator, continued participation is no longer in the patient's best interests.
- Lost to follow-up.
- Other.

In the event of pregnancy, female subjects must be discontinued from the study. 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.

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9.8 Early Discontinuation of the Study

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

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

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

9.9 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 TAK-659 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. The timing of PK and pharmacodynamics assessments as specified in the Schedule of Events (Appendix A, Table 3 and Table 4) is not flexible. 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 sponsor clinician or designee.

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.

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10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

a) Results in **death.**

b) 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).

c) Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).

d) 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).

e) Is a **congenital anomaly/birth defect**.

f) 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

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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 14 June 2010 [1]. Clarification should be made between an SAE and an AE that is considered severe or life-threatening 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 or life-threatening AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

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

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SAE Reporting Contact Information

PPD

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

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

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010 [1]. The criteria are provided in the study manual.

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

10.3 Monitoring of AEs and Period of Observation

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

a) AEs will be reported from the time of signing of the ICF through 28 days after administration of the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.

b) Serious PTEs 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.

c) Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF through 28 days after administration of the last dose of study drug and recorded in the 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 due to a patient's stable or chronic condition or intercurrent illness(es).

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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 e-mail 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
PPD			

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

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

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

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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.

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11.0 STUDY-SPECIFIC COMMITTEES

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

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12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit 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 patient's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least

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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.

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13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) 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.

A data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods.

Statistical analyses will be performed separately for each combination arm. Within each combination arm, analysis will be done by TAK-659 dose and overall.

- ***Cohort A:*** TAK-659 + bendamustine.
- ***Cohort B:*** TAK-659 + bendamustine + rituximab.
- ***Cohort C:*** TAK-659 + gemcitabine.
- ***Cohort D:*** TAK-659 + lenalidomide.
- ***Cohort E:*** TAK-659 + ibrutinib.

13.1.1 Analysis Sets

The analysis sets will include the following:

- ***Safety analysis set:*** patients who have received at least 1 dose of study drug will be used for all safety analyses and for some efficacy analyses.
- ***PK analysis set:*** patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.
- ***Response-evaluable analysis set:*** patients who have received at least 1 dose of study drug, have sites of measurable disease at baseline, and 1 post-baseline disease assessment will be used for analyses of response.
- ***DLT-evaluable analysis 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 dose of TAK-659, is observed for ≥1 cycle following the dose on Cycle 1 Day 1 and is considered to have sufficient safety data by both 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 descriptively. Variables to be analyzed include gender, age, race, weight, height, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

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13.1.3 Efficacy Analysis

Efficacy is not the primary endpoint for this study. Secondary efficacy endpoints include ORR, DOR, TTP, and PFS (for patients in the Cohort B expansion phase). No formal statistical tests will be performed for these secondary endpoints. Analyses for these endpoints will be done for each of the 5 combination arms (except PFS will be analyzed for the Cohort B expansion phase only), separately and by dose level.

- ORR is defined as the proportion of patients who achieved CR and PR (determined by the investigator) in the response-evaluable population.
- DOR is defined as the time from the date of the first documented response to the date of first documented PD by the investigator.
- TTP is defined as the time from the date of first study drug administration to the date of first documented PD by the investigator.
- PFS is defined as the time from the date of first study drug administration to the date of first documented PD or death due to any cause, whichever occurs first.

Analyses of efficacy measures will be descriptive. Antitumor activity of TAK-659 will be based on best overall response. Investigators will assess responses using the IWG criteria for malignant lymphoma. Data listings will present the tumor measurements from imaging, including changes from baseline, disease response category, and as appropriate, tumor marker measurements.

The number and percentage of patients falling into each response category will be tabulated descriptively. Estimates of CR+PR rate will be presented with 2-sided 95% exact binomial CIs.

Response rate will be tabulated by baseline 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 autologous transplant, and International Prognostic Index score. For patients with FL or MZL in the Cohort B expansion phase, PFS will be analyzed using the standard Kaplan-Meier method for survival analysis.

13.1.4 PK Analysis

The PK population will be used for the description of the plasma PK profile of TAK-659 (Cohorts A-E) and for the estimation of plasma PK parameters of TAK-659. Plasma concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods.

Plasma TAK-659 concentrations will be summarized by nominal sampling time and grouped by dose cohort and dosing cycle and day. Mean and individual plasma TAK-659 concentration data will be plotted over time and grouped by dose cohort and dosing cycle and day. Plasma concentration-time data will be used to calculate plasma PK parameters for TAK-659 by noncompartmental methods. PK parameters for TAK-659 will include, but not be limited to, C_{max}, T_{max}, C_{trough} (observed concentration at the end of a dosing interval), AUC_{τ}, CL/F (apparent clearance after extravascular administration), PTR (peak-trough ratio during a dosing interval, at steady state), and Rac (accumulation ratio).

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TAK-659 plasma PK data from the study, along with data from other studies, may contribute to population PK analyses and exposure-response analyses for pharmacodynamic, safety, and efficacy endpoints. If 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.

CCI

13.1.7 Safety Analysis

AEs will be summarized using the safety analysis set.

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

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

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Treatment-emergent AEs 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.

All AEs will be coded using MedDRA. Data will be summarized in the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs (ie, those events reported by more than 10% of all patients).
- SAEs.
- Listing of treatment-emergent AEs resulting in 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 change from baseline of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for lab parameters will be generated based on changes in NCI CTCAE grades from baseline to the worst post-baseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst post-baseline 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 analysis may be performed to most clearly enumerate rates of toxicities to further define the safety profile of TAK-659.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The dose escalation phase of this study will use a 3 + 3 design. With the exception of bendamustine, each combination drug's dose will be the dose according to the manufacturer's label. The dose of bendamustine will be based on its use in previous combination studies [3,4]. In the dose escalation phase, 9 to 12 DLT-evaluable patients from each of Cohorts A to E will be recruited based on 2 planned dose levels of TAK-659. A dose lower than 60 mg QD (eg, 40 mg QD) or intermittent QD dosing schedules (eg, 7 days on followed by 7 days off or 14 days on

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followed by 7 days off) may be evaluated in Cohort B, if appropriate. As a result, the actual number of patients to be enrolled into Cohort B will be increased accordingly. Twelve additional patients with FL or MZL will be recruited into Cohort B for the safety expansion phase; no patients from Cohorts A, C, D, or E will be recruited for the safety expansion phase since the sponsor has closed enrollment into these cohorts. Assuming a 10% dropout rate, approximately 40 patients in Cohort B, and 14 patients each in Cohorts A, C, D, and E will be recruited. The total sample size for this study will be approximately 96 patients.

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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 patient 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, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

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15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

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

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15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, 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 patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

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

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

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

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All revised ICFs must be reviewed and signed by relevant patients or the relevant patient'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 patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

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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 www.ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedules of Events

Table 1. 21-Day Cycle Schedule of Events for Cohorts A, B, and C

	Screening [a]	Cycle 1					Cycle 2				Cycles 3 and Beyond			EOT [b] (+10 days)	PFS [c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 1	Day 8	Day 15	Days 18-21	Day 1	Day 8	Day 15		
Informed consent [d]	X														
Inclusion/exclusion criteria	X														
Demographics and disease characteristics	X														
Complete 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	X			X		X				X			X	
Monitoring of concomitant medications and procedures	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first.														
AE reporting	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first.														
	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.														

Table 1. 21-Day Cycle Schedule of Events for Cohorts A, B, and C (continued)

	Screening [a]	Cycle 1					Cycle 2				Cycle 3 and Beyond			EOT [b] (+10 days)	PFS [c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 1	Day 8	Day 15	Days 18-21	Day 1	Day 8	Day 15		
Dosing															
TAK-659 administration [j]		TAK-659 is dosed PO QD.													
Bendamustine administration [k]		Bendamustine is dosed on Days 1 and 2 of each 21-day cycle, up to 8 cycles.													
Bendamustine + rituximab administration [l]		Bendamustine is dosed on Days 1 and 2 and rituximab is dosed on Day 1 of each 21-day cycle, up to 8 cycles.													
Gemcitabine administration [m]		Gemcitabine is dosed on Days 1 and 8 of each 21-day cycle.													
Patient diary review [n]		X		X	X		X		X		X		X		
Imaging/Response Assessments															
Tumor assessment for lymphomas by IWG (CT/FDG-PET/) [o]	X									X	X			X	X
Sample/Laboratory Assessments															
Hematology/chemistry [p,q]	X	X		X	X		X		X		X		X		
Urinalysis [r,s]	X				X		X				X			X	
Pregnancy test [s]	X	X					X				X			X	
Ophthalmic exam [t]	X						X				X			X	
CCI [redacted]															

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Table 1. 21-Day Cycle Schedule of Events for Cohorts A, B, and C (continued)

	Screening [a]	Cycle 1					Cycle 2				Cycle 3 and Beyond			EOT [b] (+10 days)	PFS [c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 1	Day 8	Day 15	Days 18-21	Day 1	Day 8	Day 15		
Blood samples for PK [v]		See Appendix A, Table 3 and Table 4													
CCI [redacted]															
Bone marrow biopsy and aspirate [aa]	X													X [z]	
CMV testing [aa]	X	Day 1 of each cycle												X	

AE: adverse event; ALC: absolute leukocyte count; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CMV: cytomegalovirus; CO_2: carbon dioxide; CPK: creatine phosphokinase; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment visit; FDG: fluoro-2-deoxy-D-glucose; FL: follicular lymphoma; GGT: gamma glutamyltransferase; ICF: informed consent form; IV: intravenous(ly); IWG: International Working Group; LDH: lactate dehydrogenase; MZL: marginal zone lymphoma; PCR: polymerase chain reaction; PD: pharmacodynamic(s); PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PO: oral(ly); PTE: pretreatment event; QD: once daily; SAE: serious adverse event; WBC: white blood cell; WOCBP: women of childbearing potential.
Cohort A: TAK-659 + bendamustine; Cohort B: TAK-659 + bendamustine + rituximab; Cohort C: TAK-659 + gemcitabine.

[a] Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified. A bone marrow biopsy and aspirate performed within 6 weeks before Cycle 1 Day 1 will qualify as baseline assessment.

[b] The EOT visit 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. Subsequent anticancer therapy should not be initiated before recovery from all treatment-emergent toxicities associated with TAK-659 and combination drug.

[c] For patients with FL or MZL who discontinue treatment for any reason other than PD in the Cohort B expansion phase, 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.

[d] Informed consent may be captured before the screening period (28 days before first dose).

[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 and will include a neurological exam and smoking history. Complete physical exams will also be performed on Day 1 of each cycle 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 Cycles 2, 3, and 4.

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[f] Weight should be obtained at screening, on Day 1 predose of each cycle, and at EOT.
[g] Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1, 3, and 8 (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.
[h] 12-lead ECGs will be performed as detailed in Section 9.4.8. All scheduled ECGs should be performed at predose, unless otherwise specified in Appendix A, Table 3 and Table 4 for Cycle 1.
[i] Including serious PTEs; see Section 10.0.
[j] TAK-659 will be administered PO QD for 21-day cycles. The option to modify the schedule of drug administration to include alternative schedules will be based on the review of the available PK, safety, and other clinical data by the investigators and the sponsor.
[k] Bendamustine is to be administered at 90 mg/m^2 IV as a 10- or 60-minute infusion (depending on which formulation is used) on Days 1 and 2 of each 21-day cycle, up to 8 cycles. Bendamustine should be administered after the dose of TAK-659 is taken, and the infusion should start within 15 minutes after the dose of TAK-659 is administered.
[l] Bendamustine is to be administered at 90 mg/m^2 IV as a 10- or 60-minute infusion (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 is to be administered IV per local guidelines and labeling on Day 1 of each 21-day cycle, up to 8 cycles. On days (ie, Day 1) in which all 3 agents (TAK-659, bendamustine, and rituximab) are given, TAK-659 should be administered first, followed by the bendamustine infusion (infusion to begin within 15 minutes after the TAK-659 dose). After completion of the bendamustine infusion, the rituximab infusion should be administered. On days (ie, Day 2) in which only TAK-659 and bendamustine are administered, the TAK-659 dose will be administered first, followed by the bendamustine infusion (infusion to begin within 15 minutes after the TAK-659 dose).
[m] Gemcitabine is to be administered at 1000 mg/m^2 IV as a 30-minute infusion on Days 1 and 8 of each 21-day cycle. Gemcitabine should be administered after the dose of TAK-659 is taken, and the infusion should start within 15 minutes after the dose of TAK-659 is administered.
[n] The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.
[o] Response assessments for lymphoma, including radiographic evaluation and disease symptoms, will be performed at screening, between Days 18 and 21 (predose) in Cycles 2, 4, and 6, and between Days 18 and 21 (predose) in every 3 cycles thereafter (until PD or the start of alternative therapies), and at the EOT visit. For patients with FL or MZL in the Cohort B expansion phase, response will continue to be assessed during 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. At screening, chest, abdomen, and pelvis (neck should be included, if appropriate) should be imaged by CT scan with contrast. FDG-PET scan will be performed at baseline. 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 do not need to be conducted but could be performed as clinically indicated during the study. See Section 9.4.14. If the patient has had an appropriate CT or FDG-PET scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening.
[p] The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated on Cycle 1 Day 1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBC count), lymphocytes (ALC), lymphocyte subsets (CD4, CD8, CD4:CD8 ratio), differential WBC count, and platelets. The chemistry panel consists of the following: sodium, potassium, CO_2, chloride, BUN, creatinine, CPK, bilirubin, ALP, AST, ALT, LDH, GGT, amylase, lipase, total protein, albumin, glucose, urate, calcium, phosphate, and magnesium.
[q] Laboratory assessments may be conducted within -3 days of the scheduled visit, with the exception of PK and pharmacodynamic assessments or unless otherwise noted. Day 1 visits in Cycle 2 and beyond may be modified by up to 3 days for extenuating circumstances (eg, inclement weather, holidays, vacations, or other administrative reasons).
[r] Urinalysis samples will be collected predose and analyzed at the site's local laboratory.
[s] For WOCBP only, a serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 is administered for that cycle. If a serum pregnancy test is performed within 3 days before dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1. For WOCBP only, a urine pregnancy test also will be performed at EOT.
[t] An ophthalmic exam should be performed at screening, on Cycle 2 Day 1, on Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 9.4.13 for details.

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[u] CCI [redacted]

Blood samples for plasma PK analysis will be collected as specified in Appendix A, Table 3 and Table 4.

[w] A peripheral blood sample will be obtained at screening for the purpose of genotyping patients for certain polymorphisms in genes that may be involved in the metabolism and/or disposition of TAK-659 (eg, CYP2D6).

[x] CCI [redacted]

[y] CCI [redacted]

[z] 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).

[aa] CMV serology (immunoglobulin [Ig]G and IgM) and quantitative PCR assay will be performed during screening. Quantitative PCR will be performed at Day 1 of each cycle and at the EOT visit. The CMV viral load data will be entered in the eCRF along with the local normal range for the assay. Further monitoring of CMV, if indicated, will follow the local standard practice.

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Table 2. 28-Day Schedule of Events for Cohorts D and E

	Screening [a]	Cycle 1						Cycle 2			Cycle 3 and Beyond		EOT [b] (+10 days)
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Days 22	Day 1	Day 15	
Informed consent [c]	X												
Inclusion/exclusion criteria	X												
Demographics and disease characteristics	X												
Complete medical history [d]	X	X											
Physical examination [d]	X	X		X	X		X	X	X		X	X	X
Height	X												
Weight [e]	X	X						X			X	X	X
Vital signs [f]	X	X		X	X		X	X	X		X	X	X
ECOG performance status	X	X						X			X	X	X
12-lead ECG [g]	X	X			X			X			X	X	X
Monitoring of concomitant medications and procedures	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first												
AE reporting	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first												
	SAEs [h] 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												

Footnotes are on last table page.

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Table 2. 28-Day Cycle Schedule of Events for Cohorts D and E (continued)

	Screening [a]	Cycle 1						Cycle 2			Cycle 3 and Beyond		EOT [b] (+10 days)
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 22	Day 1	Day 15	
Dosing													
TAK-659 administration [i]		TAK-659 is dosed PO QD every day.											
Lenalidomide administration [j]		Lenalidomide is dosed on Days 1-21 of a 28-day cycle.											
Ibrutinib administration [k]		Ibrutinib is dosed PO QD every day.											
Patient diary review [l]		X		X	X		X	X	X		X	X	
Imaging/Response Assessments													
Tumor assessment for lymphomas by IWG (CT/FDG-PET/) [m]	X									X	X		X
Sample/Laboratory Assessments													
Hematology/chemistry [n, o]	X	X		X	X		X	X	X		X	X	
Urinalysis (for hematuria and proteinuria evaluation) [o, p]	X				X			X			X		X
Pregnancy test [q]	X	X						X			X		X
Ophthalmic exam [r]	X							X			X		X
CCI [redacted]													
Blood samples for PK [t]		X	X	X	X	X							
CCI [redacted]													

Footnotes are on last table page.

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Table 2. 28-Day Cycle Schedule of Events for Cohorts D and E (continued)

	Screening [a]	Cycle 1						Cycle 2			Cycle 3 and Beyond		EOT [b] (+10 days)
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 22	Day 1	Day 15	
CCI [redacted]													
Bone marrow biopsy and aspirate [x]	X												
CMV testing [y]	X	Day 1 of each cycle											X

AE: adverse event; ALC: absolute leukocyte count; ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CMV: cytomegalovirus; CO_2: carbon dioxide; CPK: creatine phosphokinase; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment visit; FDG: fluoro-2-deoxy-D-glucose; FL: follicular lymphoma; GGT: gamma glutamyltransferase; ICF: informed consent form; IV: intravenous(ly); IWG: International Working Group; LDH: lactate dehydrogenase; MZL: marginal zone lymphoma; PCR: polymerase chain reaction; PD: pharmacodynamic(s); PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PO: oral(ly); PTE: pretreatment event; QD: once daily; SAE: serious adverse event; WBC: white blood cell; WOCBP: women of childbearing potential.
Cohort D: TAK-659 + lenalidomide; Cohort E: TAK-659 + ibrutinib.

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

[b] The EOT visit 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. Subsequent anticancer therapy should not be initiated before recovery from all treatment-emergent toxicities associated with TAK-659 and combination drugs.

[c] Informed consent may be captured before the screening period (28 days before first dose).

[d] 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 and will include a neurological exam and smoking history. Complete physical exams will also be performed on Day 1 of each cycle 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 Cycles 2, 3, and 4.

[e] Weight should be obtained at screening, on Day 1 predose of each cycle, and at EOT.

[f] Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1, 3, and 8 (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.

[g] 12-lead ECGs will be performed as detailed in Section 9.4.8. All scheduled ECGs should be performed at predose, unless otherwise specified in Appendix A, Table 3 and Table 4 for Cycle 1.

[h] Including serious PTEs; see Section 10.0.

[i] TAK-659 will be administered PO QD in 28-day cycles. The option to modify the schedule of drug administration to include alternative schedules will be based on the review of the available PK, safety, and other clinical data by the investigators and the sponsor.

[j] Lenalidomide is to be administered orally at 25 mg QD on Days 1-21 of a 28-day cycle. Lenalidomide should be administered after the dose of TAK-659 is taken and should be taken within 15 minutes after the dose of TAK-659 is administered.

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[k] Ibrutinib is to be administered PO at 560 mg QD in 28-day cycles. Ibrutinib should be administered after the dose of TAK-659 is taken and should be taken within 15 minutes after the dose of TAK-659 is administered.

[l] The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

[m] Response assessments for lymphoma, including radiographic evaluation and disease symptoms, will be performed at screening, between Days 22 and 29 (predose) of Cycle 2, 4, and 6, and between Days 22 and 29 (predose) of every 3 cycles thereafter (until PD or the start of alternative therapies). At screening, chest, abdomen, and pelvis (neck should be included, if appropriate) should be imaged by CT scan with contrast. FDG-PET scan should be performed at baseline. 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 do not need to be conducted but could be performed as clinically indicated during the study. See Section 9.4.14. If the patient has had an appropriate CT or FDG-PET scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at screening.

[n] The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated on Cycle 1 Day 1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBC count), lymphocytes (ALC), lymphocyte subsets (CD4, CD8, CD4:CD8 ratio), differential WBC count, and platelets. The chemistry panel consists of the following: sodium, potassium, CO_2, chloride, BUN, creatinine, CPK, bilirubin, ALP, AST, ALT, LDH, GGT, amylase, lipase, total protein, albumin, glucose, urate, calcium, phosphate, and magnesium.

[o] Laboratory assessments may be conducted within -3 days of the scheduled visit, with the exception of PK and pharmacodynamic assessments or unless otherwise noted. Day 1 visits of Cycle 2 and beyond may be modified by up to 3 days for extenuating circumstances (eg, inclement weather, holidays, vacations, or other administrative reasons).

[p] Urinalysis samples will be collected predose and analyzed at the site's local laboratory.

[q] For WOCBP only, a serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 is administered for that cycle. If a serum pregnancy test is performed within 3 days before dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1. For WOCBP only, a urine pregnancy test also will be performed at EOT.

[r] An ophthalmic exam should be performed at screening, on Cycle 2 Day 1, on Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 9.4.13 for details.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[w] CCI [redacted]

[x] 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).

[y] CMV serology (IgG and IgM) and quantitative PCR assay will be performed during screening. Quantitative PCR will be performed at Day 1 of each cycle and at the EOT visit. The CMV viral load data will be entered in the eCRF along with the local normal range for the assay. Further monitoring of CMV, if indicated, will follow the local standard practice.

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Table 3. Cycle 1 ECG, Pharmacodynamics, and PK Schedule for TAK-659 in Cohorts A to E (Dose Escalation Phase)

	Cycle 1									
	Day 1			Day 2	Day 8		Day 15			Day 16
	Single ECG	PD	PK	PK	PD	PK	Single ECG	PD [a]	PK [a]	PK [a]
Predose (within 1 hr before dosing on all days) [b]	X	X	X	X (24 hrs after Day 1 dose ±1 hr) [c]	X	X [c]	X	X	X [c]	X (24 hrs after Day 15 dose ±1 hr) [c]
0.5 hr postdose (±10 min)			X						X	
1 hr postdose (±10 min)			X						X	
2 hrs postdose (±10 min)	X		X				X		X	
2 to 4 hrs postdose					X [d]	X [d]		X [e]		
4 hrs postdose (±30 min)			X						X	
8 hrs postdose (±30 min)			X						X	

ECG: electrocardiogram; PD: pharmacodynamic(s); PK: pharmacokinetic(s).
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. All prespecified time points for ECG, PK, and pharmacodynamic collection should be relative to the dosing time of TAK-659.
[a] Scheduled PD and PK measurements on Cycle 1 Day 15 and Day 16 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off or 14 days on followed by 7 days off.
[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 (and ibrutinib and lenalidomide) dose at home. The oral study drug doses will be administered in the clinic after collection of all predose samples.
[c] The timing of the predose PK samples on Days 2, 8, 15, and 16 should be encouraged to occur at approximately the same time as the TAK-659 dosing times on the previous days of the cycle to ensure that samples represent trough samples.
[d] Scheduled PD and PK measurements at 2-4 hrs postdose on Cycle 1 Day 8 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off.
[e] On Day 15, samples for PD assessment consist of a predose sample and a 2- to 4-hour postdose sample; the postdose sample should be collected when the 2-hour or the 4-hour postdose PK sample is collected.

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Table 4. Cycle 1 ECG, Pharmacodynamics, and PK Schedule for TAK-659 in Cohort B (Safety Expansion Phase)

	Cycle 1								Cycle 2 [a]	Cycle 3 [a]	Cycle 4 [a]
	Day 1			Day 8		Day 15			Day 1 or 8 [b]	Day 1 or 8 [b]	Day1 or 8 [b]
	Single ECG	PD	PK	PD	PK	Single ECG	PD [c]	PK [c]	PK	PK	PK
Predose (within 1 hr before dosing on all days) [d, e]	X	X	X	X	X	X	X	X	X	X	X
2 hrs postdose (±10 min)	X					X					
2 to 4 hrs postdose			X	X [f]	X [f]		X	X			

ECG: electrocardiogram; PD: pharmacodynamic(s); PK: pharmacokinetic(s).
Note: When the timing of a PK, PD, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples. All prespecified time points for ECG, PK, and PD collections should be relative to the dosing time of TAK-659.
[a] Refer to Appendix A Table 1 for 12-lead ECG measurements beyond Cycle 1.
[b] Predose PK samples on Cycle 2 to Cycle 4 will be taken on Day 1 when TAK-659 is administered with continuous dosing. Predose PK samples on Cycle 2 to Cycle 4 will be taken on Day 8 when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off or 14 days on followed by 7 days off.
[c] Scheduled PD and PK measurements on Cycle 1 Day 15 and Day 16 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off or 14 days on followed by 7 days off.
[d] 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 oral study drug dose will be administered in the clinic after collection of all predose samples.
[e] The timing of the predose PK samples (Cycle 1 Day 8 and Day 15, Cycle 2 to Cycle 4 Day 1) should be encouraged to occur at approximately the same time as the TAK-659 dosing times on the previous days of the cycle to ensure that samples represent trough samples.
[f] Scheduled PD and PK measurements at 2 to 4 hours postdose on Cycle 1 Day 8 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off.

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Appendix B Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential patients, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR (Code of Federal Regulations) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
8. Obtain valid informed consent from each patient who participates in the study and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
9. 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.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

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11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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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, US, and Japan), including the following:

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

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

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

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

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

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Appendix D 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, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

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Appendix E Cockcroft-Gault Equation

For male patients:

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

For female patients:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

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Appendix F 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:

a) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
   - oral
   - intravaginal
   - transdermal

b) progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
   - oral
   - injectable
   - implantable [2]

c) intrauterine device (IUD)[2]

d) intrauterine hormone-releasing system (IUS)[2]

e) bilateral tubal occlusion[2]

f) vasectomised partner[2,3]

g) 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:

a) progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

b) male or female condom with or without spermicide[5]

c) cap, diaphragm or sponge with spermicide[5]

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

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

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

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

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

(5) 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.

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Appendix G New York Heart Association Classification of Cardiac Disease

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

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

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Appendix H Medications, Supplements, and Food Products to be Avoided or Used Cautiously

Table 1. Strong CYP3A Inhibitors or Inducers and/or P-gp Inhibitors or Inducers (Applicable to Combination Arms A-E)

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

Footnotes are on the following page.

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[a] Note that the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/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 P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer but is not on the list, then its use must be discussed on a case-by-case basis with the medical monitor or designee to assess the relative benefit and risk.
[b] Note that medications used to treat HIV or hepatitis C infection that are strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.
[c] Also inhibitor of P-gp.
[d] Withdrawn from the US market due to safety reasons.
[e] Not marketed in the US.

Table 2. Moderate CYP3A Inhibitors or Inducers (for Ibrutinib Combination Arm [Cohort E] Only)

Medication, Supplement, or Food Product [a, b]	Required Washout Period Before First Dose
Moderate CYP3A Reversible Inhibitors aprepitant ciprofloxacin fluconazole	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)
Moderate CYP3A Mechanism-based Inhibitors Diltiazem [c] erythromycin [c] verapamil [c]	7 days, or 5 times the inhibitor half-life, whichever is longer
Seville oranges	5 days
Moderate CYP3A Inducers bosentan modafinil nafcillin	7 days, or 5 times the inducer half-life, whichever is longer

[a] Note that the list of moderate CYP3A inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/Development Resources/DrugInteractionsLabeling/ucm080499.htm). If a medication, supplement, or food/beverage is suspected or known to be a moderate 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 asses the relative benefit and risk.
[b] Note that medications used to treat HIV or hepatitis C infection that are moderate CYP3A inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.
[c] Diltiazem, erythromycin, and verapamil are also P-gp inhibitors. For patients in the ibrutinib combination arm, the washout period for moderate CYP3A mechanism-based inhibitors should be followed instead of the washout period for P-gp inhibitors.

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Table 3. CYP1A2 Inhibitors and Inducers to be Used Cautiously (for Bendamustine Combination Arms [Cohorts A and B] only) [a, b]

Strong CYP1A2 Inhibitors	**Moderate CYP1A2 Inducers**
ciprofloxacin	montelukast
enoxacin	smoking
fluvoxamine	
Moderate CYP1A2 Inhibitors	
methoxsalen	
mexiletine	
oral contraceptives	
phenylpropanolamine	
thiabendazole	
zileuton	

[a] Note that the list of CYP1A2 inhibitors and inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ DrugInteractionsLabeling/ucm080499.htm).

[b] Note that medications used to treat HIV or hepatitis C infection that are CYP1A2 inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.

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Appendix I Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Added Investigational New Drug (IND) number and EudraCT number to title page.

The primary change occurs on the title page.

Added text: **IND Number:119,231 EudraCT Number: 2016-001426-34**

Rationale for change: To comply with Takeda medical writing guidelines.

Change 2: Revised background to include information on FL, update description of TAK-659, reorganize nonclinical pharmacology information for TAK-659 combination therapy, and update clinical data for TAK-659.

The primary change occurs in Section 4.1 Background.

Initial text:

4.1 Background

4.1.1 Diseases Under Study

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing about 40% of all NHL. [5] It is estimated that approximately 66,000 new cases of NHL, and consequently, approximately 20,000 new cases of DLBCL, are diagnosed annually in the United States (US) [6]. DLBCL is a form of aggressive B-cell NHL and is invariably fatal without treatment.

The immunochemotherapy regimen R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone with rituximab) is the standard treatment for patients newly diagnosed with DLBCL [7,8]. This regimen results in complete remission in approximately 65% to 75% of first-line patients with DLBCL. It is considered curative in a subset of patients, with a cure rate of >50% [9.10]. However, DLBCL is highly heterogeneous in histology, clinical behavior, and underlying biology, and therefore exhibits significant variation with regard to outcome after therapy.

High-dose chemotherapy, including salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), and autologous stem cell transplant (ASCT) are the treatments 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.

4.1.2 Study Drug

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4.1.2.1 TAK-659

TAK-659 is a potent and reversible inhibitor of spleen tyrosine kinase (SYK) being developed for oncology indications, the pathogeneses of which are either driven by or significantly contributed to by SYK-mediated signaling. TAK-659 inhibits SYK-purified enzyme with a concentration producing 50% inhibition (IC_{50}) of 3.2 nM. TAK-659 demonstrated a more than 50-fold selectivity for SYK over 290 other protein kinases screened. In cultured human tumor cells, TAK-659 potently inhibited SYK activity in hematopoietic-derived cell lines (Section 4.1.3). TAK-659 is currently being investigated as a single agent in trials of patients with NHL and acute myelogenous leukemia (AML).

…

4.1.3 Nonclinical Experience

TAK-659 is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FLT3. SYK is a nonreceptor tyrosine kinase with SH2-binding domains that bind to phosphorylated immunoreceptor tyrosine-based activation-motifs (ITAMs) located on B and T cells and certain natural killer (NK) cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells, and abnormal function of SYK has been implicated in NHL, including follicular lymphoma (FL), DLBCL, and MCL. TAK-659 inhibits SYK-purified enzyme with an IC_{50} of 3.2 nM and a concentration producing half-maximal response (EC_{50}) ranging from 25 to 400 nM in sensitive cell systems. Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models, including the OCI-Ly10 model, an 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 FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including gemcitabine, bendamustine, ibrutinib, and lenalidomide. All combination drugs were given concomitantly in nonclinical studies.

Gemcitabine HCl is a nucleoside analogue that primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. In DLBCL, gemcitabine is used to treat relapsed and refractory patients. TAK-659 has shown synergistic antitumor activity when combined with gemcitabine in nonclinical models of DLBCL. In the TMD8 model, TAK-659 (60 mg/kg once daily [QD]) in combination with gemcitabine (5 mg/kg, every 3 days times 4) achieved significant antitumor activity with tumor growth inhibition (TGI) of 96.7% (change in area under the concentration-time curve [ΔAUC], $p<0.001$), demonstrating enhanced therapeutic potential over single-agent treatment. This

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combination was found to be additive in the OCI-Ly10 model with TGI of 90.6% (ΔAUC, $p<0.001$).

Ibrutinib is an inhibitor of BTK that is approved in CLL, MCL, Waldenström's Macroglobulinemia and marginal zone lymphoma and is currently in clinical trials for DLBCL. It is hypothesized that targeting BTK, which lies downstream of SYK, in combination with SYK inhibition could lead to a more pronounced response in hematologic malignancies. In nonclinical animal models of DLBCL, the combination of TAK-659 (60 mg/kg QD) with ibrutinib (6 mg/kg QD) has shown synergistic antitumor activity. In the OCI-Ly10 ABC DLBCL model, TAK-659 in combination with ibrutinib was found to have significant antitumor activity with TGI of 68.8% (ΔAUC, $p<0.001$) when compared with vehicle, resulting in a statistically significant therapeutic advantage over single-agent treatments.

Bendamustine is a standard-of-care agent used in combination with rituximab as a second-line (or greater) therapy to treat patients with DLBCL. TAK-659 (60 mg/kg QD) in combination with bendamustine (1 mg/kg twice weekly) in the OCI-Ly10 model resulted in significant antitumor activity with TGI of 78.6% (ΔAUC, $p<0.001$) when compared with vehicle. This combination resulted in additive antitumor activity in the OCI-Ly19 GCB DLBCL model where TAK-659 (60 mg/kg QD) and bendamustine (2 mg/kg twice weekly) resulted in TGI of 52.1% (ΔAUC, $p<0.01$).

Lenalidomide is an immunomodulatory agent that has been shown to modulate different components of the immune system by altering cytokine production, regulating T-cell co-stimulation, and augmenting the NK cell cytotoxicity. The immunomodulatory properties of lenalidomide are implicated in its clinical efficacy and provide a rationale for combination with TAK-659. Combination of these agents in nonclinical studies has shown strongly additive tumor inhibition in the OCI-Ly10 DLBCL model. TAK-659 (60 mg/kg QD) in combination with lenalidomide (10 mg/kg QD) resulted in TGI of 73.1% (ΔAUC, $p<0.001$).

Overall, data from nonclinical sources support the potential for TAK-659 to be an effective agent in treating patients with relapsed or refractory DLBCL in combination with gemcitabine, bendamustine, ibrutinib, or lenalidomide.

4.1.4 Clinical Experience

Three different data cutoff dates were used to provide the most current clinical information given that the ongoing studies are in various stages of execution. The most current disposition data for Studies C34001, C34002, and C34003 are provided by the 22 October 2016 data cutoff date. The most current safety and efficacy data for Study C34001 are provided as of the 07 October 2016 data cutoff date. The most current safety and efficacy data for Study C34002 are provided as of the 18 September 2016 data cutoff date.

As of 22 October 2016, 111 patients had been dosed with TAK-659 in 3 ongoing

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studies, including 82 patients in the first-in-human (FIH) Study C34001, 26 patients in Study C34002, and 3 patients in Study C34003.

In Study C34001, the TAK-659 dose was escalated from 60 to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [15 patients], and 120 mg [7 patients]). The maximum tolerated dose (MTD) for patients with lymphoma and solid tumors was determined to be 100 mg QD. Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 82 patients treated in this study (60 lymphoma, 19 solid tumors, and 3 CLL), 63 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included PD (37 patients), adverse events (AEs; 13 patients), protocol deviation (1 patient), symptomatic deterioration (4 patients), and other (8 patients).

In Study C34002, the TAK-659 dose had been escalated from 60 to 160 mg across a total of 26 patients, and the MTD/RP2D has not yet been determined. Of the 26 patients treated in this study, 16 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included PD (3 patients), AEs (10 patients), withdrawal by subject (1 patient), and other (2 patients).

In Study C34003, the TAK-659 dose has been evaluated in 3 patients at 60 mg with plans to escalate to 100 mg. At the time of the data cutoff, all 3 patients were still on study.

The reported AEs were generally as expected based on preclinical toxicology findings with TAK-659 and the patient population being studied. In Study C34001, as of 07 October 2016, the most common (reported in ≥20% of patients) treatment-related AEs in Study C34001 have been aspartate aminotransferase (AST) increased (35 patients [44%]), amylase increased (27 patients [34%]), lipase increased (22 patients [28%]), alanine aminotransferase (ALT) increased (19 patients [24%]), fatigue (18 patients [23%]), and diarrhea (17 patients [21%]). The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (15 patients [19%]), neutropenia (12 patients [15%]), hypophosphatemia (9 patients [11%]), lipase increased (8 patients [10%]), anemia (7 patients [9%]), blood creatine phosphokinase (CPK) increased (6 patients [8%]), and pyrexia (4 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase increased, AST and ALT increased, and blood CPK increased.

There were 20 on-study deaths. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated varicella, and respiratory failure in the presence of *Pneumocystis jiroveci* pneumonia [PJP]; cytomegalovirus [CMV] and aspergillus infection; and right pneumothorax and

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renal failure). The other causes of deaths included PD (8 patients), pneumonia and sepsis (2 patients each), and hypoxia, pulmonary embolism, hepatic encephalopathy due to PD, ascites, and septic shock (1 patient each).

In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment based on investigator report as of 07 October 2016. Eight patients with DLBCL achieved a complete response (CR), and 4 achieved a partial response (PR). Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut.

In Study C34002, as of 18 September 2016, there were 7 on-study deaths, none of which was deemed treatment related. To date, the safety profile in Study C34002 appears similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both their peripheral blast and bone marrow blast counts; however, no formal responses as per International Working Group (IWG) 2003 criteria [2] have been reported as of the cutoff date.

4.1.4.1 Clinical Pharmacokinetics of TAK-659

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

Among patients with relapsed/refractory lymphoma, TAK-659 exhibited fast absorption (T_{max} [time of first occurrence of C_{max} (maximum observed concentration)] of 2 hours on Days 1 and 15 of Cycle 1). Approximate steady-state PK conditions appeared to be achieved by Cycle 1 Day 8 upon comparison of predose (trough) concentrations available during Cycle 1. Geometric mean values of steady-state, dose-normalized area under the plasma concentration–time curve during the dosing interval (AUC_{τ}/Dose) were similar across the 60 to 100 mg range, suggesting no obvious deviation from dose proportionality. Moderate variability was observed in AUC_{τ}/Dose when pooled across the 60 to 120 mg dose range (coefficient of variation of 30% for Day 1 and 50% for Day 15).

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

The mean ratio of TAK-659 renal clearance to apparent oral clearance was 0.34.

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

Amended text:

4.1 Background

4.1.1 Diseases Under Study

~~Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing about 40% of all NHL.[5] It is estimated that approximately 66,000 new cases of NHL, and consequently, approximately 20,000 new cases of DLBCL, are diagnosed annually in the United States (US) [6]. DLBCL is a form of aggressive B-cell NHL and is invariably fatal without treatment.~~ **Non-Hodgkin lymphoma (NHL), is the most common hematologic malignancy and consists of numerous subtypes [5]; it is one of the most common cancers in the United States (US), accounting for about 4% of all cancers [6]. In 2018, an estimated 74,680 new cases of NHL are expected to be diagnosed in the US, and an estimated 19,910 people will die of this disease [7]. The two most common types of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). DLBCL accounts for about 1 of every 3 lymphomas, and FL accounts for about 1 of every 5 lymphomas in the US [8].**

The immunochemotherapy regimen R-CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone with rituximab) is the standard treatment for patients **with** newly diagnosed ~~with~~ DLBCL ~~[7,8]~~**[5,6]**. This regimen results in complete remission in approximately 65% to 75% of first-line patients with DLBCL. It is considered curative in a subset of patients, with a cure rate of >50% ~~[9,10]~~**[7,8]**. However, DLBCL is highly heterogeneous in histology, clinical behavior, and underlying biology, and therefore exhibits significant variation with regard to outcome after therapy.

High-dose chemotherapy, including salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), and autologous stem cell transplant (ASCT) are the treatments 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.

Follicular lymphoma (FL) is the most common indolent NHL in the Western hemisphere, representing 20% of NHL cases [9]. Randomized clinical trials

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have demonstrated that the addition of rituximab to standard chemotherapy induction has improved overall survival. Maintenance rituximab strategies can improve progression-free survival (PFS). Bendamustine combined with rituximab has rapidly become a standard frontline strategy in North America and parts of Europe. However, ~~clinically meaningful benefit is rarely achieved in patients with progressive disease (PD) following multiple regimens.~~**several unmet needs remain, including the identification of high-risk patients at diagnosis and the development of predictive biomarkers for targeted agents [10].**

4.1.2 Study Drug

4.1.2.1 TAK-659

TAK-659 is a ~~potent and reversible inhibitor of~~**small molecule that inhibits** spleen tyrosine kinase (SYK) ~~being developed for oncology indications, the pathogeneses of which are either driven by or significantly contributed to by SYK-mediated signaling~~**and FMS-like tyrosine kinase 3 (FLT3) and is currently under development for the treatment of patients with advanced malignancies**. TAK-659 inhibits SYK- **and FLT3-**purified ~~enzyme~~**enzymes** with a concentration producing 50% inhibition (IC_{50}) of 3.2 nM **and 4.6 nM, respectively**. TAK-659 demonstrated a more than 50-fold selectivity for SYK over 290 other protein kinases screened. In cultured human tumor cells, TAK-659 potently inhibited SYK activity in hematopoietic-derived cell lines (Section 4.1.3). TAK-659 is currently being investigated as a single agent in trials of patients with NHL and acute myelogenous leukemia (AML)**, as well as a combination agent in patients with lymphoma and solid tumors**.

…

4.1.3 Nonclinical Experience

4.1.3.1 Nonclinical Pharmacology Experience With TAK-659

TAK-659 is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FLT3. SYK is a nonreceptor tyrosine kinase with SH2-binding domains that ~~bind~~**binds** to phosphorylated immunoreceptor tyrosine-based activation-motifs (ITAMs) located **within receptors found** on B and T cells and certain ~~natural killer (~~NK~~)~~ cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells, and abnormal function of SYK has been implicated in NHL, including ~~follicular lymphoma (FL)~~**FL**, DLBCL, and MCL.

TAK-659 inhibits SYK-purified enzyme with an IC_{50} of 3.2 nM and a concentration producing half-maximal response (EC_{50}) ranging from 25 to 400 nM in sensitive cell systems. Nonclinically, TAK-659 has exhibited significant antitumor activity in

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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 FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including ~~gemcitabine,~~ bendamustine, ~~ibrutinib, and~~**gemcitabine,** lenalidomide**, and ibrutinib**. All combination drugs were given concomitantly in nonclinical studies.

Refer to the TAK-659 IB for additional information.

4.1.3.2 Nonclinical Pharmacology Experience With Combination Drugs

Bendamustine is a standard-of-care agent used in combination with rituximab as a second-line (or greater) therapy to treat patients with DLBCL. TAK-659 (60 mg/kg once daily [QD]) in combination with bendamustine (1 mg/kg twice weekly) in the OCI-Ly10 model resulted in significant antitumor activity with tumor growth inhibition (TGI) of 78.6% (change in area under the concentration-time curve [ΔAUC], p<0.001) when compared with vehicle. This combination resulted in additive antitumor activity in the OCI-Ly19 GCB DLBCL model where TAK-659 (60 mg/kg QD) and bendamustine (2 mg/kg twice weekly) resulted in TGI of 52.1% (ΔAUC, p<0.01).

Gemcitabine HCl is a nucleoside analogue that primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. In DLBCL, gemcitabine is used to treat relapsed and refractory patients. TAK-659 has shown synergistic antitumor activity when combined with gemcitabine in nonclinical models of DLBCL. In the TMD8 model, TAK-659 (60 mg/kg ~~once daily [~~QD~~]~~) in combination with gemcitabine (5 mg/kg, every 3 days times 4) achieved significant antitumor activity with ~~tumor growth inhibition (~~TGI~~)~~ of 96.7% ~~(change in area under the concentration-time curve [ΔAUC]~~ **ΔAUC**, p<0.001), demonstrating enhanced therapeutic potential over single-agent treatment. This combination was found to be additive in the OCI-Ly10 model with TGI of 90.6% (ΔAUC, p<0.001).

Lenalidomide is an immunomodulatory agent that has been shown to modulate different components of the immune system by altering cytokine production, regulating T-cell co-stimulation, and augmenting the NK cell cytotoxicity. The immunomodulatory properties of lenalidomide are implicated in its clinical efficacy and provide a rationale for combination with TAK-659. Combination of these agents in nonclinical studies has shown strongly additive tumor inhibition in the OCI-Ly10 DLBCL model. TAK-659 (60 mg/kg QD) in combination with lenalidomide (10 mg/kg QD) resulted in TGI of 73.1% (ΔAUC, p<0.001).

Ibrutinib is an inhibitor of BTK that is approved in CLL, MCL, ~~Waldenström's~~

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~~Macroglobulinemia~~**WM,** and marginal zone lymphoma and is currently in clinical trials for DLBCL. It is hypothesized that targeting BTK, which lies downstream of SYK, in combination with SYK inhibition could lead to a more pronounced response in hematologic malignancies. In nonclinical animal models of DLBCL, the combination of TAK-659 (60 mg/kg QD) with ibrutinib (6 mg/kg QD) has shown synergistic antitumor activity. In the OCI-Ly10 ABC DLBCL model, TAK-659 in combination with ibrutinib was found to have significant antitumor activity with TGI of 68.8% (ΔAUC, p<0.001) when compared with vehicle, resulting in a statistically significant therapeutic advantage over single-agent treatments.

~~Bendamustine is a standard-of-care agent used in combination with rituximab as a second-line (or greater) therapy to treat patients with DLBCL. TAK-659 (60 mg/kg QD) in combination with bendamustine (1 mg/kg twice weekly) in the OCI-Ly10 model resulted in significant antitumor activity with TGI of 78.6% (ÄAUC, p<0.001) when compared with vehicle. This combination resulted in additive antitumor activity in the OCI-Ly19 GCB DLBCL model where TAK-659 (60 mg/kg QD) and bendamustine (2 mg/kg twice weekly) resulted in TGI of 52.1% (ΔAUC, p<0.01).~~

~~Lenalidomide is an immunomodulatory agent that has been shown to modulate different components of the immune system by altering cytokine production, regulating T-cell co-stimulation, and augmenting the NK cell cytotoxicity. The immunomodulatory properties of lenalidomide are implicated in its clinical efficacy and provide a rationale for combination with TAK-659. Combination of these agents in nonclinical studies has shown strongly additive tumor inhibition in the OCI-Ly10 DLBCL model. TAK-659 (60 mg/kg QD) in combination with lenalidomide (10 mg/kg QD) resulted in TGI of 73.1% (ΔAUC, p<0.001).~~

Overall, data from nonclinical sources support the potential for TAK-659 to be an effective agent in treating patients with relapsed or refractory DLBCL in combination with ~~gemcitabine,~~ bendamustine, ~~ibrutinib, or~~**gemcitabine,** lenalidomide**, or ibrutinib**.

4.1.4 Clinical Experience

~~Three different data cutoff dates were used to provide the most current clinical information given that the ongoing studies are in various stages of execution. The most current disposition data for Studies C34001, C34002, and C34003 are provided by the 22 October 2016 data cutoff date. The most current safety and efficacy data for Study C34001 are provided as of the 07 October 2016 data cutoff date. The most current safety and efficacy data for Study C34002 are provided as of the 18 September 2016 data cutoff date.~~

~~As of 22 October 2016, 111 patients had been dosed with TAK-659 in 3 ongoing studies, including 82 patients in the first-in-human (FIH) Study C34001, 26 patients in Study C34002, and 3 patients in Study C34003.~~

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In Study C34001, the TAK-659 dose was escalated from 60 to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [15 patients], and 120 mg [7 patients]). The maximum tolerated dose (MTD) for patients with lymphoma and solid tumors was determined to be 100 mg QD. Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 82 patients treated in this study (60 lymphoma, 19 solid tumors, and 3 CLL), 63 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included PD (37 patients), adverse events (AEs; 13 patients), protocol deviation (1 patient), symptomatic deterioration (4 patients), and other (8 patients).

In Study C34002, the TAK-659 dose had been escalated from 60 to 160 mg across a total of 26 patients, and the MTD/RP2D has not yet been determined. Of the 26 patients treated in this study, 16 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included PD (3 patients), AEs (10 patients), withdrawal by subject (1 patient), and other (2 patients).

In Study C34003, the TAK-659 dose has been evaluated in 3 patients at 60 mg with plans to escalate to 100 mg. At the time of the data cutoff, all 3 patients were still on study.

The reported AEs were generally as expected based on preclinical toxicology findings with TAK-659 and the patient population being studied. In Study C34001, as of 07 October 2016, the most common (reported in ≥20% of patients) treatment-related AEs in Study C34001 have been aspartate aminotransferase (AST) increased (35 patients [44%]), amylase increased (27 patients [34%]), lipase increased (22 patients [28%]), alanine aminotransferase (ALT) increased (19 patients [24%]), fatigue (18 patients [23%]), and diarrhea (17 patients [21%]). The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (15 patients [19%]), neutropenia (12 patients [15%]), hypophosphatemia (9 patients [11%]), lipase increased (8 patients [10%]), anemia (7 patients [9%]), blood creatine phosphokinase (CPK) increased (6 patients [8%]), and pyrexia (4 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase increased, AST and ALT increased, and blood CPK increased.

There were 20 on-study deaths. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated varicella, and respiratory failure in the presence of *Pneumocystis jiroveci* pneumonia [PJP]; cytomegalovirus [CMV] and aspergillus infection; and right pneumothorax and renal failure). The other causes of deaths included PD (8 patients), pneumonia and sepsis (2 patients each), and hypoxia, pulmonary embolism, hepatic encephalopathy

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~~due to PD, ascites, and septic shock (1 patient each).~~

~~In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment based on investigator report as of 07 October 2016. Eight patients with DLBCL achieved a complete response (CR), and 4 achieved a partial response (PR). Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut.~~

~~In Study C34002, as of 18 September 2016, there were 7 on-study deaths, none of which was deemed treatment related. To date, the safety profile in Study C34002 appears similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both their peripheral blast and bone marrow blast counts; however, no formal responses as per International Working Group (IWG) 2003 criteria [2] have been reported as of the cutoff date.~~

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). All 7 studies are ongoing.

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

New Table 4.a Overview of TAK-659 Clinical Studies

4.1.4.2 ~~4.1.4.1~~ Clinical Pharmacokinetics of TAK-659

~~Preliminary pharmacokinetic (PK) results are available at the 60 to 120 mg dose range evaluated in the dose escalation portion of Study C34001.~~ Preliminary plasma **pharmacokinetics (**PK**)** results are available ~~for 34 patients (17~~**from** lymphoma, ~~17~~ solid tumor~~) after single dosing~~**,** and ~~for 25~~**AML** patients ~~(14 lymphoma, 11 solid tumor) after repeated QD dosing for 15 days;~~**enrolled in Studies C34001 and C34002. In addition,** preliminary urine PK results are available from ~~19 patients (12~~ lymphoma~~, 7~~ **and** solid tumor~~). Among patients with relapsed/refractory lymphoma, TAK-659 exhibited~~ **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 upon comparison of predose (trough) concentrations available during Cycle 1. Geometric mean values of steady-state, dose-~~**) 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

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~~(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 of ~~30% for Day 1 and 50% for Day 15).~~**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.**

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

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

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

Rationale for changes: To better describe the prevalence of the types of NHL, including DLBCL and FL, and for consistency with TAK-659 IB Edition 5.1.

Change 3: Reorganized and updated potential benefits and risks of TAK-659.

The primary change occurs in Section 4.1.5 Benefits and Risks.

Initial text: **4.1.5 Benefits and Risks**

TAK-659 had been administered to a total of only 111 patients as of 22 October

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2016, and it is not currently possible to identify and describe with certainty the adverse effects of the compound.

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.

Potential risks based on clinical observations:

On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, asymptomatic lipase elevations are reported commonly (≥10%). Patients in Study C34005 will have frequent monitoring of amylase as outlined in the Schedules of Events (Appendix A).

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 potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

The benefits of TAK-659 have not been established; however, early signs of clinical antitumor activity were seen. In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment per investigator report as of 07 October 2016. Eight patients with DLBCL achieved a CR and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL

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achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut.

Further details regarding the benefits and risks associated with TAK-659 may be found in the current version of the TAK-659 Investigator's Brochure (IB).

The risks associated with the administration of bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib should be referenced in accordance with their respective United States Package Inserts (USPIs) [11-13, 15-17] or applicable labeling.

TAK-659 has not been administered in combination previously in NHL. The combination of TAK-659 and other agents (bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib) may lead to exacerbation of known toxicities of single-agent administration for each agent, and possibly the occurrence of new toxicities that have not been identified with the single agents.

4.1.5.1 Potential Overlapping Toxicities for the Combination of TAK-659 and Combination Partners

Because the combination of TAK-659 with any of the combination agents (bendamustine, rituximab, gemcitibine, lenalidomide, and ibrutinib) has not yet been tested in humans, there are no identified risks for each of the combinations, and all reported AEs are considered unexpected for the purposes of regulatory reporting.

4.1.5.2 Drug-Drug Interaction Risk Assessment for the Combination of TAK-659 and Combination Partners

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 P-glycoprotein (P-gp) and is metabolized by cytochrome P450 (CYP) 3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.40%, respectively. Consequently, there is a potential risk for TAK-659 PK to be altered by drugs that are strong CYP3A inhibitorChns or inducers or P-gp inhibitors or inducers.

<u>Assessment of TAK-659 as Victim of DDIs</u>

Based on data included in their respective USPIs [11-13,15-17] or applicable labeling, bendamustine, rituximab, gemcitabine, and lenalidomide are not expected to inhibit or induce CYP3A or P-gp at clinically relevant doses; therefore, it is unlikely for co-administration of these agents to cause alterations in TAK-659 PK.

However, at clinically relevant doses, ibrutinib has the potential to inhibit the efflux transporter P-gp in the gastrointestinal (GI) tract at higher local concentrations that may be achieved after PO administration. Thus, the systemic exposures of oral narrow therapeutic index P-gp substrates may be increased upon

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co-administration of ibrutinib because of decreased intestinal efflux and increased bioavailability of the oral P-gp substrate. Because in vitro data indicate that TAK-659 is a P-gp substrate, there is a theoretical risk of increased TAK-659 systemic exposure with ibrutinib co-administration (gut P-gp inhibitor) relative to TAK-659 administration alone. Based on current literature, the majority of clinical DDIs due to P-gp inhibition are associated with approximately 2-fold or lower increases in the exposures of P-gp substrates.

For all combination arms, the TAK-659 starting dose (60 mg QD) will be less than the single-agent MTD of 100 mg QD determined among patients with solid tumors and lymphoma. Dose escalation will proceed to 100 mg QD (maximally administered dose [MAD]) only if safety and tolerability of the 60 mg dose is demonstrated. If appropriate, intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may also be evaluated if supported by safety and preliminary TAK-659 PK findings.

Amended text:

4.1.5 Benefits and Risks

~~TAK-659 had been administered to a total of only 111 patients as of 22 October 2016, and it is not currently possible to identify and describe with certainty the adverse effects of the compound.~~

4.1.5.1 Potential Benefits and Risks of TAK-659

Potential Benefits of TAK-659

Clinical benefit has been observed in Study C34001. Response data were available for 85 patients (11 solid tumor, 58 DLBCL, 12 indolent NHL, and 4 CLL) as of 22 October 2017 in Study C34001. Among response-evaluable patients with solid tumors, 1 patient (9%) experienced a partial response (PR) and 1 patient (9%) had a response of stable disease (SD) at the time of the data cutoff. Among response-evaluable patients with lymphoma DLBCL, best responses of CR and PR were reported for 11 and 6 patients, respectively. Of the 17 patients with DLBCL who responded, 2 had transitioned to stem cell transplant before the data cutoff; 39 patients with DLBCL were still receiving study drug as of the data cutoff. Ten patients had a best response of SD, and 31 patients experienced progressive disease (PD). Among the 4 response-evaluable patients with CLL, 2 patients achieved PR and 2 had SD. Nine patients with indolent lymphomas responded to treatment with TAK-659. Three patients achieved a CR, 6 patients achieved PR, and 2 patients had SD.

Potential ~~risks from nonclinical studies~~***Risks From Nonclinical Studies*** *in* ~~dogs~~***Dogs*** *and* ~~rats include:~~ ***Rats***

- Lymphoid/hematopoietic effects that include lymphoid depletion and myelosuppression that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased

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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.

Potential ~~risks based on clinical observations:~~ ***Risks Based on Clinical Observations***

- ~~On the basis of~~**Based on** data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. ~~In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage.~~ In clinical studies to date, asymptomatic lipase elevations are reported commonly (≥10%). Patients in Study C34005 will have frequent monitoring of **lipase and** amylase as outlined in the Schedules of Events (Appendix A).
- 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 potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.
- ~~The benefits of TAK-659 have not been established; however, early signs of clinical antitumor activity were seen. In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment per investigator report as of 07 October 2016. Eight patients with DLBCL achieved a CR and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut.~~
- **There have been occurrences of opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PJP), in some patients who had fever.**

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These patients had other underlying conditions that made them prone to 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 treatment-emergent adverse event (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 TEAE (26%) and the most frequently reported SAE (15%). Cytomegalovirus (CMV) infection (20%) and sepsis (17%) were also frequently reported TEAEs. Sepsis (17%) and pneumonia (15%) were the most frequently reported Grade ≥3 TEAEs.**

Further details regarding the benefits and risks associated with TAK-659 may be found in the ~~current version of the~~ TAK-659 ~~Investigator's Brochure (IB)~~**IB**.

4.1.5.2 Potential Benefits and Risks of Combination Drugs

The **benefits and** risks associated with the administration of bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib should be referenced in accordance with their respective ~~United States~~**US** Package Inserts (USPIs) [11-13,15-17] or applicable labeling.

TAK-659 has ~~not~~ been ~~administered~~**investigated** in combination ~~previously in NHL~~**with other agents in Studies C34003, C34005, and C34008, and preliminary activity has been observed (see TAK-659 IB)**. The combination of TAK-659 and other agents **in this study** (bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib) may lead to exacerbation of known toxicities of single-agent administration for each agent, and possibly the occurrence of new toxicities that have not been identified with the single agents.

~~4.1.5.1~~ *Potential Overlapping Toxicities for the Combination of TAK-659 and Combination ~~Partners~~**Drugs***

Because the ~~combination of TAK-659 with any of the combination agents (bendamustine, rituximab, gemcitibine, lenalidomide, and ibrutinib) has not yet been tested in humans, there are no identified risks for each of the combinations, and all reported AEs are considered unexpected for the purposes of regulatory reporting.~~ **study is ongoing, and the safety data are limited, no identified risks for each of the combination agents in this study have been confirmed. Expectedness will be assessed using the respective approved reference safety information (RSI).**

~~4.1.5.2~~ *Drug-Drug Interaction Risk Assessment for the Combination of TAK-659 and Combination ~~Partners~~**Drugs***

No formal PK drug-drug interaction (DDI) studies have been conducted with

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TAK-659 in humans. In vitro studies indicate that TAK-659 is a substrate of P-glycoprotein (P-gp) and is metabolized by cytochrome P450 (CYP) 3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.40%, respectively. Consequently, there is a potential risk for TAK-659 PK to be altered by drugs that are strong CYP3A inhibitors or inducers or P-gp inhibitors or inducers.

Assessment of TAK-659 as Victim of DDIs

Based on data included in their respective USPIs [11-13,15-17] or applicable labeling, bendamustine, rituximab, gemcitabine, and lenalidomide are not expected to inhibit or induce CYP3A or P-gp at clinically relevant doses; therefore, it is unlikely for co-administration of these agents to cause alterations in TAK-659 PK.

However, at clinically relevant doses, ibrutinib has the potential to inhibit the efflux transporter P-gp in the gastrointestinal (GI) tract at higher local concentrations that may be achieved after PO administration. Thus, the systemic exposures of oral narrow therapeutic index P-gp substrates may be increased upon co-administration of ibrutinib because of decreased intestinal efflux and increased bioavailability of the oral P-gp substrate. Because in vitro data indicate that TAK-659 is a P-gp substrate, there is a theoretical risk of increased TAK-659 systemic exposure with ibrutinib co-administration (gut P-gp inhibitor) relative to TAK-659 administration alone. Based on current literature, the majority of clinical DDIs due to P-gp inhibition are associated with approximately 2-fold or lower increases in the exposures of P-gp substrates.

~~For all combination arms, the TAK-659 starting dose (60 mg QD) will be less than the single-agent MTD of 100 mg QD determined among patients with solid tumors and lymphoma. Dose escalation will proceed to 100 mg QD (maximally administered dose [MAD]) only if safety and tolerability of the 60 mg dose is demonstrated. If appropriate, intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may also be evaluated if supported by safety and preliminary TAK-659 PK findings.~~

Rationale for change: For consistency with TAK-659 IB Edition 5.1.

Change 4: Reorganized and updated study rationale.

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

Initial text: **4.2 Rationale for the Proposed Study**

TAK-659 is an orally bioavailable, potent and reversible inhibitor of SYK and FLT3. SYK is a nonreceptor tyrosine kinase with SH2-binding domains that bind to phosphorylated ITAMs located on B and T cells and certain NK cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and

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proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells and abnormal function of SYK has been implicated in NHL, including FL, DLBCL, and MCL. TAK-659 inhibits SYK purified enzyme with an IC_{50} of 3.2 nM and an EC_{50} ranging from 25 to 400 nM in sensitive cell systems. Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models including the OCI-Ly10 model, an ABC-DLBCL model; the OCI-Ly19 model, a GCB-DLBCL model; the PHTX-95L model, a primary human DLBCL model; the RL FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including gemcitabine, bendamustine, ibrutinib, and lenalidomide. With regard to clinical activity, in Study C34001 as of the data cutoff date of 07 October 2016, 17 of the 48 response-evaluable patients responded to treatment. Eight patients with DLBCL achieved a CR, and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut.

...

4.2.1 Rationale for Dose and Schedule Selection

TAK-659 has been evaluated as a single agent given PO on a continuous daily dosing schedule in its FIH dose escalation study (C34001) in patients with advanced solid tumors or lymphoma. Four dose levels (60, 80, 100, and 120 mg QD) have been evaluated in Study C34001, and the MTD has been determined to be 100 mg QD. Following the safety expansion of the 100 mg cohort, Study C34001 is currently in the dose expansion phase, evaluating the efficacy, safety, and tolerability of TAK-659 administered at the 100 mg dose level in 5 different cohorts of B-lymphocyte malignancies. Early signs of clinical activity in lymphoma have been demonstrated across all doses evaluated. As of the 07 October 2016 data cutoff, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment per investigator report. Eight patients with DLBCL achieved a CR, and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut. These responses have been observed at doses of 60 (1 PR), 80 (1 PR), 100 (8 CRs and 7 PRs), and 120 mg QD (1 PR). These data suggest that doses in the tolerable dose range of 60 to 100 mg are pharmacologically active. Preliminary data show that TAK-659 exhibits an acceptable PK profile across the 60 to 100 mg dose levels that supports continuous QD dosing. On the basis of the available safety and tolerability data, the AEs observed with TAK-659 treatment overall are reversible and manageable. The

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laboratory abnormalities, such as lipase, amylase, and liver function test elevations, were asymptomatic.

In addition, TAK-659 is being evaluated as a single agent in relapsed/refractory AML in Study C34002, which includes phase 1b dose escalation and phase 2 dose expansion phases. Currently, the 60 mg starting dose of TAK-659 has been determined to be safe and tolerable, and dose escalation is ongoing at the 160 mg dose level.

In this dose escalation study, the starting dose of TAK-659 will be 60 mg QD in combination with a fixed dose regimen of each combination drug. Dose escalation of TAK-659 will follow a standard 3+3 escalation scheme. On the basis of the dose escalation experience with TAK-659 in Studies C34001 and C34002, dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg QD dose is demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may be evaluated on the basis of safety, tolerability, and preliminary PK and efficacy data if available following agreement between investigators and the sponsor. However, the dose of TAK-659 cannot be escalated beyond 100 mg, which is the MTD for single-agent TAK-659 in solid tumors and lymphoma.

The dose and schedule at which bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib will be administered will be in accordance with their respective USPIs [11-13, 15-17] or applicable labeling, unless otherwise specified. The dose of bendamustine (90 mg/m^2) is based on its use in previous combination studies with rituximab in both indolent NHL and DLBCL [3,4].

4.2.2 Rationale for PK Assessments

For all dose escalation cohorts (including the safety expansion in the MTD/MAD/RP2D cohorts), serial blood samples will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15 to characterize the plasma PK of TAK-659 when administered with each of the combination partners. Specifically, serial plasma PK assessments will be used to describe single- and repeat-dose concentration-time profiles of TAK-659 and calculate PK parameters. In addition, blood samples for plasma PK will be collected at the same time points for cytokine/chemokine assessments on Cycle 1 Day 8. All plasma PK data may additionally contribute to population PK model development for TAK-659. The major aim of PK assessments in this study is to compare exposures of TAK-659 following co-administration with each combination partner with exposures observed following single-agent administration. Specifically, PK data from this combination study will be compared with historical single-agent exposures observed in Study C34001 to determine whether there are clinically meaningful differences in TAK-659 PK between the single-agent and combination settings in patients with lymphoma.

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Additionally, plasma PK data collected in the dose escalation cohorts may be used individually or in combination with data from other studies to explore the relationship between TAK-659 PK and pharmacodynamic effects, pharmacogenomics in drug-metabolizing enzymes and/or transporters, safety parameters, and clinical response.

CCI

[redacted]

Amended text:

4.2 Rationale for the Proposed Study

4.2.1 Rationale for the Combination of TAK-659 + Combination Drugs

TAK-659 is an orally bioavailable, potent and reversible inhibitor of SYK and FLT~~3.~~**3 and is currently under development for the treatment of patients with advanced malignancies (eg, NHL).** SYK is a nonreceptor tyrosine kinase with SH2-binding domains that bind to phosphorylated ITAMs located on B and T cells and certain NK cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously in hematopoietic cells and abnormal function of SYK has been implicated in NHL, including FL, DLBCL, and MCL. TAK-~~-~~659 inhibits SYK purified enzyme with an IC_{50} of 3.2 nM and an EC_{50} ranging from 25 to 400 nM in sensitive cell systems.

Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models including the OCI-Ly10 model, an ABC-DLBCL model; the OCI-~~-~~Ly19 model, a GCB-DLBCL model; the PHTX-95L model, a primary human DLBCL model; the RL FL model; and the MINO MCL model. TAK-659 has been tested in nonclinical DLBCL models in combination with a number of agents used in the relapsed/refractory setting, including gemcitabine, bendamustine, ibrutinib, and lenalidomide. ~~With regard to clinical activity, in Study C34001 as of the data cutoff date of 07 October 2016, 17 of the 48 response-evaluable patients responded to treatment. Eight patients with DLBCL achieved a CR, and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL~~

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~~achieved a PR with a second achieving PR after the datacut.~~

Early signs of clinical activity of TAK-659 have been observed in the first-in-human (FIH) Study C34001 in patients with multiple subtypes of NHL. In this study, response data were available for 85 patients (11 solid tumor, 58 DLBCL, 12 iNHL, and 4 CLL). Among response-evaluable patients with solid tumors, 1 patient (9%) had experienced a PR. Among response-evaluable patients with DLBCL, best responses of CR and PR were reported for 11 and 6 patients, respectively. Clinical activity in responding DLBCL patients was achieved independent of cell of origin subtype (GCB or non-GCB) or disease history (de novo or transformed) [18]. Refer to the TAK-659 IB for detailed clinical information.

...

4.2.2 ~~4.2.1~~ Rationale for Dose and Schedule Selection

4.2.2.1 Rationale for the Dose and Schedule of TAK-659

TAK-659 has been evaluated as a single agent given PO on a continuous daily dosing schedule in its FIH dose escalation study (C34001) in patients with advanced solid tumors or lymphoma. Four dose levels (60, 80, 100, and 120 mg QD) have been evaluated in Study C34001, and the MTD has been determined to be 100 mg QD. Following the safety expansion of the 100 mg cohort, Study C34001 is currently in the dose expansion phase, evaluating the efficacy, safety, and tolerability of TAK-659 administered at the 100 mg dose level in 5 different cohorts of B~~-~~-lymphocyte malignancies. Early signs of clinical activity in lymphoma have been demonstrated across all doses evaluated. ~~As of the 07 October 2016 data cutoff, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 MCL), 17 patients had responded to treatment per investigator report. Eight patients with DLBCL achieved a CR, and 4 achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR with a second achieving PR after the datacut. These responses have been observed at doses of 60 (1 PR), 80 (1 PR), 100 (8 CRs and 7 PRs), and 120 mg QD (1 PR). These data suggest that doses in the tolerable dose range of 60 to 100 mg are pharmacologically active. Preliminary data show that TAK-659 exhibits an acceptable PK profile across the 60 to 100 mg dose levels that supports continuous QD dosing. On the basis of the available safety and tolerability data, the AEs observed with TAK-659 treatment overall are reversible and manageable. The laboratory abnormalities, such as lipase, amylase, and liver function test elevations, were asymptomatic.~~

~~In addition~~**Currently**, TAK-659 is being evaluated as ~~a single agent in relapsed/refractory AML in Study C34002, which includes phase 1b dose~~

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~~escalation and phase 2 dose expansion phases. Currently, the 60 mg starting dose of TAK-659 has been determined to be safe and tolerable, and dose escalation is ongoing at the 160 mg dose level.~~ **in combination with nivolumab (Study C34003) and venetoclax (Study C34008). Based on the dose escalation experience with TAK-659 in Studies C34001, C34003, and C34008, dosing of TAK-659 will escalate in 20 mg increments up to 100 mg QD provided that the safety and tolerability of the 60 mg QD dose is demonstrated. Alternative dose regimens (eg, intermittent QD dosing of 7 days on followed by 7 days off, or 14 days on followed by 7 days off), or dose levels below the starting dose of 60 mg (eg, 40 mg) may be evaluated based on safety, tolerability, and preliminary PK and efficacy data, if available, following agreement between investigators and the sponsor. The dose of TAK-659 cannot be escalated beyond 100 mg, which is the MTD for single-agent TAK-659 in solid tumors and lymphoma.**

In this dose escalation study, the starting dose of TAK-659 will be 60 mg QD in combination with a fixed dose regimen of each combination drug. Dose escalation of TAK-659 will follow a standard 3 + 3 escalation scheme. ~~On the basis of the dose escalation experience with TAK-659 in Studies C34001 and C34002, dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg QD dose is demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may be evaluated on the basis of safety, tolerability, and preliminary PK and efficacy data if available following agreement between investigators and the sponsor. However, the dose of TAK-659 cannot be escalated beyond 100 mg, which is the MTD for single-agent TAK-659 in solid tumors and lymphoma.~~

4.2.2.2 Rationale for the Dose and Schedule of Combination Drugs

The dose and schedule at which bendamustine, rituximab, gemcitabine, lenalidomide, and ibrutinib will be administered will be in accordance with their respective USPIs [11-13,15-17] or applicable labeling, unless otherwise specified. The dose of bendamustine (90 mg/m^2) is based on its use in previous combination studies with rituximab in both indolent NHL and DLBCL [3,4].

4.2.3 ~~4.2.2~~ Rationale for PK Assessments

~~For all dose escalation cohorts (including the safety expansion in the MTD/MAD/RP2D cohorts), serial blood samples will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15 to characterize the plasma PK of TAK-659 when administered with each of the combination partners. Specifically, serial plasma PK assessments will be used to describe single- and repeat-dose concentration-time profiles of TAK-659 and calculate PK parameters. In addition, blood samples for plasma PK will be collected at the same time points for cytokine/chemokine assessments on Cycle 1 Day 8. All plasma PK data may additionally contribute to population PK model development for TAK-659. The~~

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~~major~~**The primary** aim of PK ~~assessments~~**sampling** in this study is to compare exposures of TAK-659 following co-administration with each combination ~~partner~~**drug** with exposures observed following single-agent administration. Specifically, PK data from this combination study will be compared with historical single-agent exposures observed in Study C34001 to determine whether there are clinically meaningful differences in TAK-659 PK between the single-agent and combination settings in patients with lymphoma. ~~Additionally, plasma PK data collected in the dose escalation cohorts~~**In the dose escalation phase, intensive PK samples will be collected from all patients during Cycle 1, as detailed in Appendix A, Table 3. In the safety expansion part, sparse PK samples will be collected (refer to Appendix A, Table 4). Plasma PK data collected in this study** may be used individually or in combination with data from other studies to explore the relationship between TAK-659 ~~PK and pharmacodynamic effects, pharmacogenomics in drug-metabolizing enzymes and/or transporters, safety parameters, and clinical response~~**exposure and clinical**

CCI

[redacted]

Rationale for change: For consistency with TAK-659 IB Edition 5.1 and to clarify different PK sampling schemes for dose escalation and safety expansion phases.

Change 5: Revised study design to restrict the expansion phase of the study to Cohort B only, and added text to permit evaluation of intermittent once-daily (QD) dosing schedules in Cohort B if appropriate.

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

Initial text:

6.1 Overview of Study Design

This is a phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination partners (bendamustine, bendamustine+rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with advanced NHL after at least 1 prior line of therapy. The primary objective of the study is to determine the MTD or the RP2D of TAK-659 when administered with each of the combination

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partners.

During dose escalation, the dose of TAK-659 will be escalated (planned 2 dose levels of escalation: 60 and 100 mg) according to a 3+3 dose escalation scheme; all 5 combination partners will be administered at a fixed dose and regimen.

It is expected that approximately 100 patients (approximately 20 in each of the 5 treatment groups) will be enrolled in the study.

Once enrolled in the study, patients will be assigned to one of 5 treatment groups comprising TAK-659 in combination with bendamustine, bendamustine+rituximab, gemcitabine, lenalidomide, or ibrutinib. The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg dose has been demonstrated (Section 8.3). Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) also may be evaluated if appropriate. Dose escalation will continue until the MTD is reached, or until TAK-659 100 mg QD (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Approximately 6 additional patients will be enrolled at the MTD/MAD/RP2D for each combination for further safety evaluation.

The dose of each combination drug will remain constant while the TAK-659 dose escalation takes place. The doses of the combination drugs will be as follows:

- Bendamustine: 90 mg/m^2 administered intravenously (IV) over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles.
- Bendamustine+rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab administered IV per local guidelines and labeling on Day 1 of a 21-day cycle, up to 8 cycles.
- Gemcitabine: 1000 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle.
- Lenalidomide: 25 mg PO QD for Days 1 to 21 of a 28-day cycle.
- Ibrutinib: 560 mg PO QD of a 28-day cycle.

Amended text:

6.1 Overview of Study Design

This is a phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination ~~partners~~**drugs** (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with advanced NHL after at least 1 prior line of therapy. The primary objective of the study is to determine the MTD or the RP2D of TAK-659 when administered with each of the

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combination ~~partners.~~

~~During dose escalation, the dose of TAK-659 will be escalated (planned 2 dose levels of escalation: 60 and 100 mg) according to a 3+3 dose escalation scheme; all 5 combination partners will be administered at a fixed dose and regimen.~~

~~It is expected that approximately 100 patients (approximately 20 in each of the 5 treatment groups) will be enrolled in the study.~~ **drugs.** Once enrolled in the study, patients will be assigned to ~~one~~**1** of 5 ~~treatment groups comprising TAK-659 in combination with~~**cohorts:**

- **Cohort A (TAK-659 + bendamustine~~,~~).**
- **Cohort B (TAK-659 + bendamustine + rituximab~~,~~).**
- **Cohort C (TAK-659 +** gemcitabine~~,~~**).**
- **Cohort D (TAK-659 +** lenalidomide~~, or~~**).**
- **Cohort E (TAK-659 +** ibrutinib**). ~~The starting~~**

This study comprises 2 phases: a dose escalation phase and a safety expansion phase. Patients in all 5 cohorts (Cohorts A-E) will participate in the dose escalation phase of the study.

During the dose escalation phase, the dose of TAK-659 will be ~~60 mg QD. Dose escalation will follow a standard 3~~**escalated (planned 3 dose levels of escalation: 60, 80, and 100 mg) according to a 3** + 3 **dose** escalation scheme~~, and dosing~~**. The dose of oral TAK-659** will increase ~~to~~**in 20 mg increments to a maximum of** 100 mg QD**,** provided that the safety and tolerability of the 60 mg dose has been demonstrated ~~(Section 8.3). Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose~~**. Dose** levels below the starting dose of 60 mg ~~(eg, 40 mg~~ **QD (eg, 40 mg QD) or intermittent QD dosing schedules (eg, 7 days on followed by 7 days off, or 14 days on followed by 7 days off**) also may be evaluated**,** if appropriate**, in Cohort B**. Dose escalation will continue until the MTD is reached, or until TAK-659 100 mg QD (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified **based** on ~~the basis of~~ the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. ~~Approximately 6~~

The doses of combination drugs will be administered at a fixed dose and regimen (see Section 8.3).

During the dose escalation phase, DLT-evaluable patients in each dose cohort will consist of patients who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The dose escalation decision is based on the DLT occurrences during Cycle 1 per the 3 + 3 escalation schema. Additionally, toxicity and tolerability beyond Cycle 1, available PK and pharmacodynamic data, and early signs of clinical activity will be taken into consideration in dose escalation decisions

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and final determination of the MTD and RP2D of TAK-659 with combination drugs in each of the cohorts. Based on the evolving data from the trial, an alternative dose escalation plan including dose, schedule, DLT evaluation period, and further expansion of a given cohort, may be subject to change following discussions and agreement between the investigators and the sponsor medical monitor.

During the safety expansion phase of the study, approximately 12 additional patients **with advanced FL or MZL** will be ~~enrolled~~**added to Cohort B** at the MTD/MAD/RP2D for ~~each combination for~~ further safety evaluation. **PK samples will be collected at prespecified time points to characterize the PK of TAK-659 when administered with each of the combination drugs. No patients from Cohorts A, C, D, or E will enter the safety expansion phase of the study because effective 16 March 2018, the sponsor closed recruitment into Cohorts C, D, and E, and effective 16 October 2018, the sponsor closed recruitment into Cohort A.**

~~The dose of each combination drug will remain constant while the TAK-659 dose escalation takes place. The doses of the combination drugs will be as follows:~~

- ~~Bendamustine: 90 mg/m^2 administered intravenously (IV) over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles.~~
- ~~Bendamustine+rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab administered IV per local guidelines and labeling on Day 1 of a 21-day cycle, up to 8 cycles.~~
- ~~Gemcitabine: 1000 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle.~~
- ~~Lenalidomide: 25 mg PO QD for Days 1 to 21 of a 28-day cycle.~~
- ~~Ibrutinib: 560 mg PO QD of a 28-day cycle.~~

Rationale for change: To streamline the text due to the closure of Cohorts A, C, D and E, clarify the dose escalation rationale, and allow additional dosing regimens to be evaluated in Cohort B.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 8.1.2 Cohort B (TAK-659 + Bendamustine/Rituximab) Dosing Regimen.

Section 13.3 Determination of Sample Size.

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Appendix A Schedules of Events Table 3 and Table 4 footnotes.

Change 6: Restricted study population in Cohort B expansion phase to patients with advanced FL or MZL.

The primary change occurs in Section 7.1 Inclusion Criteria.

Initial text: 2. Histologically or cytologically confirmed diagnosis of advanced NHL of any histology (with the exception of patients with WM and CLL).

Amended text: 2. ~~Histologically~~**In the dose escalation phase, histologically** or cytologically confirmed diagnosis of advanced NHL of any histology (with the exception of patients with WM and CLL). **In the safety expansion phase for Cohort B, only patients with advanced FL or MZL will be included.**

Rationale for change: To align the patient population in the Cohort B expansion phase with the TAK-659 clinical development strategy.

Section 2.0 STUDY SUMMARY also contains this change.

Change 7: Revised study sample size determination and planned enrollment numbers for each cohort.

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

Initial text: **13.3 Determination of Sample Size**

The dose escalation of this study will use a 3+3 design. With the exception of the bendamustine combination arm, the combination partner's dose will be the dose according to the manufacturer's label. The dose of bendamustine will be based on its use in previous combination studies [3,4]. The planned doses of TAK-659 are 60 and 100 mg. For each combination arm, 9 to 12 DLT-evaluable patients will be needed for the dose escalation portion. In addition, for each arm, another 6 patients will be needed for safety expansion. Assuming a 10% dropout rate, 20 patients will be needed for each arm; therefore, the total sample size for this study, including all 5 arms, will be 100.

Amended text: **13.3 Determination of Sample Size**

The dose escalation **phase** of this study will use a 3 + 3 design. With the exception of ~~the~~ bendamustine ~~combination arm, the~~**, each** combination ~~partner~~**drug's** dose will be the dose according to the manufacturer's label. The dose of bendamustine will be based on its use in previous combination studies [3,4]. ~~The planned doses of TAK-659 are 60 and 100 mg. For each combination arm~~**In the dose escalation phase**, 9 to 12 DLT-evaluable patients ~~will be needed for the dose escalation portion. In addition, for each arm, another 6 patients will be needed for safety expansion~~**from each of Cohorts A to E will be recruited based on 2 planned dose levels of TAK-659. A dose lower than 60 mg QD (eg, 40 mg QD) or**

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intermittent QD dosing schedules (eg, 7 days on followed by 7 days off, or 14 days on followed by 7 days off) may be evaluated in Cohort B, if appropriate. As a result, the actual number of patients to be enrolled into Cohort B will be increased accordingly. Twelve additional patients with FL or MZL will be recruited into Cohort B for the safety expansion phase; no patients from Cohorts A, C, D, or E will be recruited for the safety expansion phase since the sponsor has closed enrollment into these cohorts. Assuming a 10% dropout rate, ~~20 patients will be needed for each arm; therefore, the~~**approximately 40 patients in Cohort B and 14 patients each in Cohorts A, C, D, and E will be recruited. The** total sample size for this study~~, including all 5 arms,~~ will be ~~100~~ **approximately 96 patients.**

Rationale for change: To update the sample size estimations to account for the additional doses/dosing regimens permitted in Cohort B and the closure of Cohorts A, C, D, and E.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.2 Number of Patients.

Change 8: Revised planned dose levels of TAK-659.

The primary change occurs in Section 8.3 Dose Escalation Rules.

Initial text: **8.3 Dose Escalation Rules**

The dose escalation phase of the study is designed to determine the DLTs and MTD and/or RP2D of TAK-659 when given in combination with bendamustine (± rituximab), gemcitabine, lenalidomide, or ibrutinib. Approximately 20 patients are expected to be enrolled in each of 5 cohorts based on the planned 2 dose-level escalation for TAK-659 (Table 8.f) when administered with a fixed-dose regimen of the combination drugs; the exact number of patients to be enrolled will depend on the actual number of dose-level cohorts required, which may deviate from the dose escalation plan based on toxicities and the PK results observed during the initial dose levels.

The dose of the combination drugs will be as follows:

- Bendamustine: 90 mg/m^2 administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles.
- Bendamustine+rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab administered IV per local guidelines and labeling on Day 1 of a 21-day cycle, up to 8 cycles.
- Gemcitabine: 1000 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of a

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21-day cycle.

- Lenalidomide: 25 mg PO QD for Days 1 to 21 of a 28-day cycle.
- Ibrutinib: 560 mg PO QD of a 28-day cycle.

…

Dose escalation of TAK-659 will not exceed 100 mg QD, the single-agent MTD for TAK-659, as established in the FIH dose escalation study of TAK-659 (C34001). More conservative dose escalation, including evaluation of an intermediate dose (eg, 80 mg QD) or de-escalation in 20 mg decrements from the starting dose of 60 mg QD of TAK-659 (eg, 40 mg) if that dose is determined to be not tolerable, expansion of an existing dose level, or an alternative regimen/schedule, are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety, for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659, or for adjustment based on the initial characterization of PK of TAK-659 when administered with the combination drugs.

…

Table 8.f Planned Dose Levels of TAK-659

Dose Level	Dose (Unit)
1	60 mg
2	100 mg (a)

More conservative dose escalation, including evaluation of intermediate doses, dose de-escalation in 20 mg decrements from the starting dose of 60 mg QD if that determined to be not tolerable, expansion of an existing dose level, and an alternative dose schedule/regimen are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659.
(a) The maximum dose to be assessed is TAK-659 100 mg QD.

…

Patients who do not meet these minimum requirements will be regarded as ineligible for DLT evaluation for the given dose cohort and may be replaced within the same cohort.

Dose escalation is planned for TAK-659 only. While the combination drugs are administered with a fixed dose and schedule, in case of frequent occurrences of dose modification or discontinuation of the combination drug in Cycle 1 and/or Cycle 2 and beyond per dose modification guidelines in Section 8.4, upon discussion and agreement between investigators and the sponsor, the fixed dose of the combination drug could be reset at a lower dose for the purpose of further evaluation and determination of the TAK-659 MTD/RP2D.

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Amended text:

8.3 Dose Escalation Rules

The dose escalation phase of the study is designed to determine the DLTs and MTD and/or RP2D of TAK-659 when given in combination with bendamustine (± rituximab), gemcitabine, lenalidomide, or ibrutinib. ~~Approximately 20 patients are expected to be enrolled in each of 5 cohorts~~**Patients in Cohorts A to E will be dosed** based on the planned ~~2~~**3** dose-level escalation for TAK-659 (Table 8.f) ~~when administered with a fixed-dose regimen~~**in each** of the combination ~~drugs; the~~**cohorts. The** exact number of patients to be enrolled will depend on the actual number of dose-level cohorts required, which may deviate from the dose escalation plan based on toxicities and the PK results observed during the initial dose levels.

The dose of the combination drugs will be as follows:

- ~~Bendamustine: 90 mg/m^2 administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles.~~
- ~~Bendamustine+rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab administered IV per local guidelines and labeling on Day 1 of a 21-day cycle, up to 8 cycles.~~
- ~~Gemcitabine: 1000 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle.~~
- ~~Lenalidomide: 25 mg PO QD for Days 1 to 21 of a 28-day cycle.~~
- ~~Ibrutinib: 560 mg PO QD of a 28-day cycle.~~

Cohort	Combination Study Drug	Dosage and Regimen
A	Bendamustine	90 mg/m^2 administered IV over 10 or 60 minutes (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 minutes (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 administered IV per local guidelines and labeling on Day 1 of each 21-day cycle, up to 8 cycles
C	Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes 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 each 28-day cycle

...

~~Dose escalation of TAK-659 will not exceed 100 mg QD, the~~**During the dose**

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escalation phase, 3 levels of dose escalation are planned for TAK-659: 60, 80, and 100 mg (Table 8.f), according to a 3 + 3 dose escalation scheme. The single-agent MTD for TAK-~~659,~~**659 is 100 mg QD** as established in the FIH dose escalation study of TAK-659 (C34001)**. Therefore, dose escalation of TAK-659 will not exceed 100 mg QD in this study**. More conservative dose escalation, including ~~evaluation of an intermediate dose (eg, 80 mg QD) or~~ de-escalation in 20 mg decrements from the starting dose of 60 mg QD of TAK-659 (eg, 40 mg **QD**) if that dose is determined to be not tolerable, expansion of an existing dose level, or an alternative regimen/schedule, are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety, for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659, or for adjustment based on the initial characterization of PK of TAK-659 when administered with the combination drugs.

…

Table 8.f Planned Dose Levels of TAK-659 for Cohorts A to E

Dose Level	Dose (Unit)
1	60 mg
2	~~100~~**80** mg ~~(a)~~
3	**100 mg** [a]

[a] **The maximum dose to be assessed is TAK-659 100 mg QD.**

…

Patients who do not meet these minimum requirements will be regarded as ineligible for DLT evaluation for the given dose cohort and may be replaced within the same cohort. ~~Dose escalation is planned for TAK-659 only. While the combination drugs are administered with a fixed dose and schedule, in case of frequent occurrences of dose modification or discontinuation of the combination drug in Cycle 1 and/or Cycle 2 and beyond per dose modification guidelines in Section 8.4, upon discussion and agreement between investigators and the sponsor, the fixed dose of the combination drug could be reset at a lower dose for the purpose of further evaluation and determination of the TAK-659 MTD/RP2D.~~

Rationale for change: To allow additional doses/dosing regimens to be evaluated in Cohort B.

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The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.1 Overview of Study Design.

Section 8.4 Dose Modification Guidelines.

Change 9: Revised duration of an individual patient's study participation.

The primary change occurs in Section 6.3.1 Duration of an Individual Patient's Study Participation.

Added text: **At the conclusion of the study, participants who continue to demonstrate clinical benefit may be eligible to receive Takeda-supplied study drug. Study drug may be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of Takeda.**

Takeda reserves the right to terminate access to Takeda supplied study drug if any of the following occurs: a) the benefit-risk profile is not favorable; b) the marketing application is rejected by responsible health authority; c) the study is terminated due to safety concerns; d) investigational agent(s) becomes commercially available or other access mechanism becomes available; e) development of the drug is suspended or ceased, or sponsor cannot adequately supply investigational agent; or f) appropriate therapeutic alternatives become available in the local market.

Rationale for change: To explain how patients who are benefitting from study drugs can continue to have access to them after they complete the study.

Change 10: Extended total study duration.

The primary change occurs in Section 6.3.4 Total Study Duration.

Initial text: **6.3.4 Total Study Duration**

It is anticipated that this study will last approximately 27 months.

Amended text: **6.3.4 Total Study Duration**

It is anticipated that this study will last approximately ~~27~~**30** months.

Rationale for change: To more accurately reflect the anticipated duration of the study.

Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting also contains this change.

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Change 11: Specified number of prior lines of therapy for patients entering Cohort B expansion phase and clarified the definition of lines of therapy.

The primary change occurs in Section 7.1 Inclusion Criteria.

Initial text:

4. Patients who are refractory or relapsed after at least 1 prior line of therapy and for whom no effective standard therapy is available per the investigator's assessment.
   - Either treatment naïve to, relapsed/refractory to, or experienced treatment failure due to other reasons with ibrutinib, idelalisib, or any other investigational BCR pathway inhibitors not directly targeting SYK.
   - Prior treatment with a regimen that includes the combination drug will not necessarily exclude a patient from that cohort if the investigator views treatment with that agent as appropriate. However, a patient who has a contraindication for a particular combination agent or who has been discontinued from prior therapy with a particular agent for toxicity will not be eligible for inclusion in that particular cohort.

Amended text:

4. ~~Patients~~ **In the dose escalation phase, patients** who are refractory or relapsed after at least 1 prior line of therapy **due to progression, intolerance, or physician/patient decision** and for whom no effective standard therapy is available per the investigator's assessment. **In the safety expansion phase for Cohort B in patients with FL or MZL, the prior line of therapy is limited to ≤1.**

   a) Either treatment naïve to, relapsed/refractory to, or experienced treatment failure due to other reasons with ibrutinib, idelalisib, or any other investigational BCR pathway inhibitors not directly targeting SYK.

   b) Preinduction salvage chemotherapy and ASCT should be considered 1 therapy.

   c) Any consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 line of therapy with the preceding combination therapy. Maintenance antibody therapy should not be considered a line of therapy.

   d) For aggressive NHL (ie, DLBCL), single-agent anti-CD20 monoclonal antibody therapy should not be considered a line of therapy. Antibody therapy in patients with indolent NHL (ie, FL) given as a single agent after disease progression from a prior treatment should be considered a line of therapy.

   e) For patients with DLBCL transformed from indolent lymphoma, any treatment received for the indolent disease before the transformation to DLBCL will, in general, not count toward the 2 to 3 prior lines of therapy

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required for DLBCL in this study.

f) Prior treatment with a regimen that includes the combination drug will not necessarily exclude a patient from that cohort if the investigator views treatment with that agent as appropriate. However, a patient who has a contraindication for a particular combination agent or who has been discontinued from prior therapy with a particular agent for toxicity will not be eligible for inclusion in that particular cohort.

Rationale for change: To clarify that patients in the Cohort B expansion may have had no more than 1 prior line of therapy, and to assist in determining the number of lines of prior therapy for study eligibility.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 5.1.2 Secondary Objectives.

Change 12: Revised method for measuring renal function.

The primary change occurs in Section 7.1 Inclusion Criteria.

Initial text:

6. Patients must have adequate organ function, including the following:

…

- Renal: creatinine clearance ≥60 mL/min either as estimated by the Cockcroft-Gault equation or based on urine collection (12 or 24 hours) (See Appendix E).

Amended text:

6. Patients must have adequate organ function, including the following:

…

c) ~~•~~ Renal: creatinine clearance ≥60 mL/min ~~either~~ as estimated by the Cockcroft-Gault equation ~~or based on urine collection (12 or 24 hours) (See~~**(see** Appendix E).

Rationale for change: To simplify the method for measuring renal function.

Section 2.0 STUDY SUMMARY also contains this change.

Change 13: Added requirement for controlled fasting serum glucose levels during screening.

The primary change occurs in Section 7.1 Inclusion Criteria.

Added text:

6. Patients must have adequate organ function, including the following:

…

iii. Fasting serum glucose level shall be controlled to 130 mg/dL during the

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screening period.

Rationale for change: Added as an additional measure of adequate organ function to determine study eligibility.

Section 2.0 STUDY SUMMARY also contains this change.

Change 14: Added requirement that women of childbearing potential must have a negative serum pregnancy test at screening.

The primary change occurs in Section 7.1 Inclusion Criteria.

Added text: 7. Female subjects who:

…

e) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) at screening.

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 15: Added requirement that female patients should not donate ova from time of signing informed consent through 180 days after last dose of study drug.

The primary change occurs in Section 7.1 Inclusion Criteria.

Added text: **8. Female patients should not donate ova from the time of signing the informed consent through 180 days after the last dose of study drug.**

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Section 8.7 Precautions and Restrictions also contains this change.

Change 16: Added requirement that male patients should not donate sperm from time of signing informed consent through 180 days after last dose of study drug.

The primary change occurs in Section 7.1 Inclusion Criteria.

Added text: **9. 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 other TAK-659 clinical study protocols.

Section 8.7 Precautions and Restrictions also contains this change.

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Change 17: Clarified exclusion criteria related to prior anticancer treatment and prior autologous stem cell transplant.

The primary change occurs in Section 7.2 Exclusion Criteria.

Initial text:

11. Systemic anticancer treatment (incluing investigational agents) or radiotherapy less than 2 weeks before the first dose of study treatment (≤4 weeks for large molecule agents).
12. Prior ASCT within 6 months or prior ASCT at any time without full hematopoietic recovery before Cycle 1 Day 1, or allogeneic stem cell transplant any time.

Amended text:

11. Systemic anticancer treatment (~~incluing~~**including** investigational agents) or radiotherapy less than 2 weeks before the first dose of study treatment (≤4 weeks for ~~large molecule agents).~~ **antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine).**
12. Prior ASCT within 6 months or prior ASCT at any time without ~~full~~**adequate** hematopoietic recovery**, defined by the entry criteria in the study,** before Cycle 1 Day 1, or allogeneic stem cell transplant any time.

Rationale for change: To more accurately describe the intent of these exclusion criteria.

Section 2.0 STUDY SUMMARY also contains this change.

Change 18: Clarified exclusion criterion related to cardiovascular conditions.

The primary change occurs in Section 7.2 Exclusion Criteria.

Initial text:

14. Patients with any of the following cardiovascular conditions are excluded:
    - Acute myocardial infarction within 6 months before starting study drug.

Amended text:

14. Patients with any of the following cardiovascular conditions are excluded:
    a) ~~• Acute~~**Unstable angina or acute** myocardial infarction within ~~6~~**12** months before starting study drug.

Rationale for change: To more accurately describe the intent of this exclusion criterion.

Change 19: Updated definitions of dose-limiting toxicity.

The primary change occurs in Section 8.2 Definitions of DLT.

Initial text:

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE version 4.03, effective 14 June 2010 [1]. These criteria are provided in the Study Manual. DLT is defined as any of the following events that are considered by the investigator to be at least

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possibly related to therapy with TAK-659 when administered in combination with bendamustine±rituximab, gemcitabine, lenalidomide, and ibrutinib. AEs in which the relationship to study drug cannot be ruled out should be considered possibly related to study drug.

- Grade 4 neutropenia (ANC <500 cells/mm^3) lasting more than 7 consecutive days.
- ≥Grade 3 neutropenia (ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as a temperature ≥38.5°C.
- Grade 4 thrombocytopenia lasting more than 7 consecutive days.
- Grade 3 thrombocytopenia of any duration accompanied by clinically significant bleeding.
- A platelet count <10,000/mm^3 at any time.
- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
- Grade 3 fatigue that lasts less than 1 week.
- ≥Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-HT antagonist and a corticosteroid given in standard doses and according to standard schedules).
- ≥Grade 3 diarrhea that can be controlled to ≤Grade 1 or baseline in 7 days with optimal supportive therapy.
- Any other Grade 3 nonhematologic toxicity that can be controlled to ≤Grade 1 or baseline in 7 days with appropriate treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor clinician.
- Inability to administer at least 75% of planned doses of study drug within Cycle 1 due to treatment-related toxicity.
- Delay in the initiation of the subsequent cycle of therapy by more than 7 days due to treatment-related hematologic or nonhematologic toxicities.
- Greater than or equal to Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug(s). In this setting, a course of action will be determined jointly by the investigators and the sponsor clinician.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment in this dose escalation study will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

Patients experiencing a DLT in Cycle 1 may continue in the study if they are deriving clinical benefit, but they will be administered reduced doses of TAK-659 and/or the combination agent as appropriate.

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Amended text:

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE version 4.03, effective 14 June 2010 [1]. These criteria are provided in the ~~Study Manual~~**study manual**. DLT is defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with TAK-~~-~~659 when administered in combination with bendamustine ± rituximab, gemcitabine, lenalidomide, and ibrutinib. AEs in which the relationship to study drug cannot be ruled out should be considered possibly related to study drug.

- **Hematologic toxicity:**
  - ~~•~~ Grade 4 neutropenia (ANC ~~<~~<500 ~~cells/mm^3) lasting~~**/µL) unresolved to Grade ≤1 (ANC >1500/µL) or baseline for** more than 7 consecutive days **in the absence of growth factor support**.
  - ~~•~~ ~~≥~~Grade ≥3 neutropenia (ANC ~~<~~<1000 ~~cells/mm^3~~**/µL**) with fever and/or infection, where fever is defined as ~~a~~**an oral** temperature ~~≥~~≥38.5~~°~~°C.
  - ~~•~~ Grade 4 thrombocytopenia ~~lasting~~**(<25,000/µL) unresolved to Grade ≤1 (>75,000/µL) or baseline for** more than 7 consecutive days **or a platelet count <10,000/µL at any time**.
- ~~•~~
  - Grade ≥3 thrombocytopenia ~~of any duration accompanied by~~**(<50,000/µL) with** clinically significant bleeding.
- ~~• A platelet count <10,000/mm^3 at any time.~~
  - **Grade 4 anemia.**
- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - ~~Grade 3 fatigue that lasts less than 1 week.~~**Fatigue or arthralgia/myalgia that improve to Grade ≤2 within 7 days.**
  - ~~Grade~~ ≥~~Grade~~ 3 nausea and/or emesis that can be controlled to ≤Grade ≤1 or baseline in 7 days with the use of optimal antiemetic prophylaxis (defined as an antiemetic regimen that employs both a 5-~~HT~~**hydroxytryptamine 3 (5-HT$_3$)** antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - ≥Grade ≥3 diarrhea that can be controlled to ≤Grade ≤1 or baseline in 7 days with optimal supportive therapy.
  - **Asymptomatic Grade 3 amylase or lipase elevations that last ≤7 days.**
  - **Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3) considered not dose limiting following agreement between the sponsor and investigators.**
  - **Isolated Grade ≥3 abnormalities of other laboratory parameters (other than electrolyte imbalances/abnormalities) that resolve to Grade ≤1 in**

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≤7 days without clinical sequelae or need for therapeutic intervention considered not dose-limiting following agreement between the sponsor and investigators.

- **Grade 3 rash lasting ≤7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.**
- Any other Grade 3 nonhematologic toxicity that can be controlled to ≤Grade ≤1 or baseline in 7 days with appropriate treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor ~~clinician~~**medical monitor**.

- —Inability to administer at least 75% of planned doses of ~~study drug~~**TAK-659** within Cycle 1 due to treatment-related toxicity.
- Delay in the initiation of the subsequent cycle of therapy by more than 7 days due to ~~treatment~~**study drug**-related hematologic or nonhematologic toxicities.
- ~~Greater than or equal to Grade 2~~**Other study drug-related** nonhematologic toxicities ~~that are considered by~~**Grade ≥2 that, in the opinion of** the investigator ~~to be related to study drug(s)~~**, require a dose reduction or discontinuation of study treatment**. In this setting, a course of action will be determined jointly by the investigators and the sponsor ~~clinician~~**medical monitor**.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment in this dose escalation study will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

Patients experiencing a DLT in Cycle 1 may continue in the study if they are deriving clinical benefit, but they will be administered reduced doses of TAK-659 and/or the combination agent as appropriate.

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 20: Revised dose modification guidelines for hematologic and nonhematologic toxicities.

The primary change occurs in Section 8.4.4 Dose Modification for Hematologic and Nonhematologic Toxicity Table 8.i, Table 8.j, Table 8.k, and Table 8.l.

Description of Change:

- In Table 8.i Dose Modification Guidelines for Hematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/Rituximab, the following changes were made:
  - Revised retreatment criteria based on ANC.

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— Revised descriptions for Grades 1-2 and Grade 3 thrombocytopenia.

— Revised retreatment criteria based on PLT count.

— Revised the description of Grade 4 anemia.

- In Table 8.j Dose Modification Guidelines for Nonhematologic Toxicities for Cohort A (TAK-659 + Bendamustine) and Cohort B (TAK-659 + Bendamustine/Rituximab, the following changes were made:

  — Revised the list of exceptions under other Grade 3 nonhematogic toxicities.

- In Table 8.k Dose Modification Guidelines for Hematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib), the following changes were made:

  — Revised retreatment criteria based on ANC.

  — Revised descriptions for Grades 1-2 and Grade 3 thrombocytopenia.

  — Revised retreatment criteria based on PLT count.

  — Revised the description of Grade 4 anemia.

- In Table 8.l Dose Modification Guidelines for Nonhematologic Toxicities for Cohort C (TAK-659 + Gemcitabine), Cohort D (TAK-659 + Lenalidomide), and Cohort E (TAK-659 + Ibrutinib), the following changes were made:

  — Revised the list of exceptions under other Grade 3 nonhematogic toxicities.

Rationale for change: Updated for accuracy.

Change 21: Revised retreatment criteria for Cohorts A, B, and C.

The primary change occurs in Section 8.4.3 Retreatment Criteria for Cohorts A, B, and C (Bendamustine or Gemcitabine).

Initial text:

8.4.3 Re-treatment Criteria for Bendamustine or Gemcitabine (Cohorts A, B, and C)

Per the prescribing information for bendamustine and gemcitabine, the patient must meet the following re-treatment criteria before starting the next dose of bendamustine (Cohorts A and B) or gemcitabine (Cohort C):

- ANC $\geq 1500/mm^3$.
- Platelet count $\geq 100{,}000/mm^3$.
- Total bilirubin <ULN, ALT/AST <1.5×ULN.

Amended text:

8.4.3 ~~**Re-treatment**~~**Retreatment Criteria for Cohorts A, B, and C (Bendamustine or Gemcitabine ~~(Cohorts A, B, and C~~)**

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Per the prescribing information for bendamustine and gemcitabine, the patient must meet the following ~~re-treatment~~retreatment criteria before starting the next dose of bendamustine (Cohorts A and B) or gemcitabine (Cohort C):

a) ~~•~~ ANC ≥~~1500/mm^3~~ **1000/µL.**

b) ~~•~~ Platelet count ≥~~100,000/mm^3~~ **75,000/ µL.**

~~• Total bilirubin <ULN, ALT/AST <1.5×ULN~~.

Rationale for change: To align with standard of care.

Section 8.4.4 Dose Modification for Hematologic and Nonhematologic Toxicity Table 8.i and Table 8.k also contain this change.

Change 22: Reorganized and updated management of TAK-659–related clinical events.

The primary change occurs in Section 8.8 Management of TAK-659–Related Clinical Events.

Initial text:

8.8 Management of Clinical Events

…

8.8.1 Prophylaxis Against Infection

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

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

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

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

Given their degree of immunosuppression, patients with posttransplant lymphoproliferative disease are often at an increased risk of developing infections. Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the patient is more 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 parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.

Amended text:

8.8 Management of TAK-659–Related Clinical Events

…

8.8.1 Prophylaxis Against Infection

Patients with advanced hematologic malignancies may be at an increased risk of infection. Prophylactic use of antibiotic, antiviral, or antifungal medication can be considered as clinically indicated and per local standard practice **or per National Comprehensive Cancer Network Prevention and Treatment of Cancer-Related Infections Guidelines**. In particular, lymphopenia can develop in association with either treatment or with the underlying disease (lymphoma). Lymphopenia can be associated with reactivation of herpes zoster, CMV, herpes simplex, and other viruses. Antiviral therapy, such as acyclovir, ~~ganciclovir~~**ganciclovir**, valacyclovir, or other antiviral agents, may be initiated as clinically indicated. ~~Testing of CMV replication by a~~ ~~**local**~~ **It is recommended that prophylaxis for varicella-zoster virus should be administered for Cohort B [19].**

Given their degree of immunosuppression, subjects with posttransplant lymphoproliferative disease are often at an increased risk of developing infections. Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the subject is more prone to developing neutropenia. Subjects who develop neutropenic fever should be evaluated promptly and treated immediately with parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.

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8.8.1.1 CMV Monitoring and Prophylaxis

At screening, on Day 1 of each treatment cycle, and at end of treatment (EOT), all subjects should have CMV serology and/or quantitative polymerase chain reaction (PCR) assay ~~will be required at Baseline, and further~~**performed. If positive at any timepoint, CMV monitoring is advised once a week with a decrease to once every cycle as it becomes negative. Interruption of study drug is generally advised if the positive CMV test is accompanied by associated clinical symptoms, if the copy number reaches a level indicates a need for treatment per institutional standard, or if the CMV test remains positive despite the antiviral treatment for CMV. Further** monitoring and prophylactic or preemptive therapy for asymptomatic patients, if indicated, should follow the institutional standard practice. The following agents ~~could~~**should** be considered for prophylaxis or pre-emptive treatment against CMV: ganciclovir (IV), valganciclovir (PO), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until CMV is no longer detected per PCR.

8.8.1.2 Prophylaxis for Opportunistic Infections

Patients with lymphopenia may also be more prone to developing infections, such as respiratory tract infections or pneumonia. Consider a diagnosis of opportunistic infection, including PJP, in patients presenting with shortness of breath, cough, or fever.

Prophylaxis for PJP must be initiated (either at ~~Baseline~~**baseline** or during treatment) if the following is present:

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

It is recommended that the prophylaxis for PJP should be implemented in Cohort B regardless of the above-mentioned conditions [19]. 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~~**baseline**, PJP prophylaxis should be considered at the start of study treatment. When steroids or any immunomodulatory agents need to be used to manage AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is ~~co-administered~~**coadministered**. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated; however, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

~~Given their degree of immunosuppression, patients with posttransplant lymphoproliferative disease are often at an increased risk of developing infections.~~

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~~Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the patient is more 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 parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.~~

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 23: Added a section heading for management of combination drug-related clinical events.

The primary change occurs in Section 8.9 Management of Combination Drug-Related Clinical Events.

Added text: **8.9 Management of Combination Drug-Related Clinical Events**

Clinical characteristics and risk mitigation measures addressing each of the important combination drug–related clinical events are summarized below. Refer to the most recent USPI [9-11, 13-15] or applicable labeling for each drug for further details.

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 24: Added sparse PK sampling schedule for Cohort B expansion phase, and clarified PK and PD sampling schedules for Cohort B when intermittent QD dosing schedule is used.

The primary change occurs in Appendix A Schedules of Events Table 3 and Table 4.

Description of change:

- The following footnotes were added to Table 3:

  [a] Scheduled PD and PK measurements on Cycle 1 Day 15 and Day 16 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off or 14 days on followed by 7 days off.

  [d] Scheduled PD and PK measurements at 2-4 hrs postdose on Cycle 1 Day 8 will be skipped when TAK-659 is administered with intermittent dosing of 7 days on followed by 7 days off.

  The following table was added:

  [New Table 4 Cycle 1 ECG, Pharmacodynamics, and PK Schedule for TAK-659 in Cohort B (Safety Expansion Phase)]

Rationale for change: To have separate PK sampling schedules for Cohort B expansion phase and to clarify PK and PD sampling schedules for intermittent dosing regimens.

Section 9.4.21 PK Measurements also contains this change.

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Change 25: Added progression-free survival (PFS) follow-up visits for patients in Cohort B expansion phase who discontinue treatment for any reason other than progressive disease.

The primary change occurs in Section 9.4.14 Disease Assessment.

Initial text:

9.4.14 Disease Assessment

Patients will undergo radiographic evaluation and symptom assessment to monitor and assess disease response. Response assessment will follow revised response criteria for malignant lymphoma per IWG [2]. CT scans (with contrast) of the neck (if appropriate), chest, abdomen, and pelvis will be performed at Screening/Baseline (within 28 days before the first study drug administration), at the end of every other cycle through Cycle 6, and at the end of every 3 cycles thereafter (until PD or the start of alternative therapies). 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 do not need to be conducted 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 unless contraindicated. The same imaging modality should be used consistently throughout the study to monitor the disease status.

Amended text:

9.4.14 Disease Assessment

Patients will undergo radiographic evaluation and symptom assessment to monitor and assess disease response. Response assessment will follow revised response criteria for malignant lymphoma per IWG **2007 criteria** [2]. CT scans (with contrast) of the neck (if appropriate), chest, abdomen, and pelvis will be performed at ~~Screening/Baseline~~ **screening/baseline** (within 28 days before the first study drug administration), at the end of every other cycle through Cycle 6~~,~~ and at the end of every 3 cycles thereafter (until PD or the start of alternative therapies), **and at the EOT visit. For patients with FL or MZL in the Cohort B expansion phase, response will continue to be assessed during 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 ~~should~~ **will** be performed ~~only at Baseline for tumor types for which it represents standard of care for response assessment~~ **at baseline**. 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,

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additional FDG-PET scans do not need to be conducted 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 unless contraindicated. The same imaging modality should be used consistently throughout the study to monitor the disease status.

Rationale for change: To be consistent with follow-up requirements and to evaluate a clinically relevant efficacy endpoint.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting.

Appendix A Schedules of Events Table 1.

Change 26: Updated procedures for cytomegalovirus monitoring.

The primary change occurs in Appendix A Schedules of Events Tables 1 and 2.

Description of Changes:

- For the row *CMV Testing*:
  - Testing was added on Day 1 of each cycle and at the EOT visit.
  - The following text was added to the associated footnote:

    [aa] CMV serology (immunoglobulin [Ig]G and IgM) and quantitative PCR assay will be performed during screening. Quantitative PCR will be performed at Day 1 of each cycle and at the EOT visit.

Rationale for change: To include CMV monitoring time points based on input from TAK-659 investigators and the recommendation from the TAK-659 Lymphoma Steering Committee to the mitigate potential risk of CMV reactivation.

The following sections also contain this change:

Section 8.8.1.1 CMV Monitoring and Prophylaxis.

Section 9.4.23 CMV Testing.

Change 27: Removed residual bone marrow sample collections from study procedures.

The primary change occurs in Section Appendix A Schedules of Events Table 1 and Table 2.

Description of change:

- The following rows have been removed:

  Residual fresh bone marrow aspirate

  Residual fresh bone marrow biopsy

Rationale for change: To reduce redundancy in study procedures.

Section 9.4.17 Bone Marrow Biopsy and Aspirate also contains this change.

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CCI

[redacted]

Pro

CCI [redacted]

Rationale for change: To enable additional pharmacodynamic analysis.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

CCI [redacted]

Appendix A Schedules of Events Table 1 footnote (y) and Table 2 footnote (w).

Change 30: Revised reasons for discontinuation of treatment with study drug.

The primary change occurs in Section 9.6 Discontinuation of Treatment With Study Drug.

Initial text: **9.6 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) during the first cycle, patients with Grade 4 nonhematologic toxicity, patients with Grade 4 anemia, and patients with other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.4 and the USPIs [11-13,15-17] or applicable labeling for the combination drugs. Discontinuation of treatment occurs only when both study drugs are required to be discontinued due to AEs.
- Protocol deviations.
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

During the dose escalation phase, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

Once study drug has been discontinued, all study procedures outlined for the EOT

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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.

Amended text:

9.6 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) during the first cycle, patients with Grade 4 nonhematologic toxicity, patients with Grade 4 anemia, and patients with other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.4 and the USPIs [11-13,15-17] or applicable labeling for the combination drugs. Discontinuation of treatment occurs only when both study drugs are required to be discontinued due to AEs.
- Protocol deviations.
- PD.
- **Occurrence of pregnancy (if applicable).**
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant
- ~~Study terminated by sponsor~~.
- Withdrawal **of consent** by ~~subject~~**patient**.
- **In the opinion of the investigator, continued use of study drug is no longer in the patient's best interests.**
- Lost to follow-up.
- **Study terminated by sponsor**.
- Other.

During the dose escalation phase, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

In the event of pregnancy, female subjects must discontinue use of study drugs. 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**, Table 1 and Table 2**). The primary reason for study drug discontinuation will be recorded on the eCRF.

Rationale for change: For consistency with other TAK-659 clinical study protocols.

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Change 31: Revised reasons for withdrawal of patients from study.

The primary change occurs in Section 9.7 Withdrawal of Patients From Study.

Initial text:

9.7 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.
- 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.

Amended text:

9.7 Withdrawal of Patients From Study

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

- AE.
- Protocol deviation.
- **Due to pregnancy.**
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal **of consent** by ~~subject~~**patient**.
- **In the opinion of the investigator, continued participation is no longer in the patient's best interests.**
- Lost to follow-up.
- Other.

In the event of pregnancy, female subjects must be discontinued from the study. 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.

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Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 32: Added criteria for early discontinuation of study.

The primary change occurs in Section 9.8 Early Discontinuation of the Study.

Added text:

9.8 Early Discontinuation of the Study

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

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

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

Rationale for change: For consistency with other TAK-659 clinical study protocols.

Change 33. Added PFS as a secondary endpoint for patients in Cohort B expansion phase.

The primary change occurs in Section 5.2.2 Secondary Endpoints.

Added text:

- **PFS (for patients in the Cohort B expansion phase).**

Rationale for change: To evaluate a clinically relevant efficacy endpoint.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures Table 6.b.

Section 13.1.3 Efficacy Analysis.

Change 34: Added a urine pregnancy test for women of childbearing potential at end of treatment for each cohort.

The primary change occurs in Appendix A Schedules of Events Tables 1 and 2.

Description of change:

- In the *Pregnancy test* row, an "X" has been added to the EOT column.
- The following text has been added to the associated footnote:

For WOCBP only, a urine pregnancy test also will be performed at EOT.

Rationale for change: To ensure examination completeness.

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Section 9.4.12 Pregnancy Test also contains this change.

Change 35. Added vital sign measurements on Day 15 of Cycle 3 and beyond for Cohorts A, B, and C.

The primary change occurs in Appendix A Schedules of Events Table 1.

Description of change:
- In the *Vital signs* row, an "X" has been added to the Cycle 3 and beyond Day 15 column.

Rationale for change: To ensure examination completeness and for consistency with Appendix A Schedule of Events Table 2.

Change 36. Updated reference citations to support background information in protocol and added reference citation for a published TAK-659 clinical study.

The primary change occurs in Section 4.1.1 Diseases Under Study and Section 4.2.1 Rationale for the Combination of TAK-659 + Combination Drugs.

Description of change:
- The following references have been removed from Section 4.1.1:
  - 5. Diffuse Large B-Cell Lymphoma. 2014 Review of Cancer Medicines on the WHO List of Essential Medicines: Union for International Cancer Control; 2014. p. 1-8.
  - 6. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Published 2010. Accessed 25 February 2013.
- The following references have been added to Section 4.1.1:
  - 5. Kumar V, Abbas A, Fausto N, Aster J. Robbins and Cotran Pathologic Basis of Disease. 8 ed. Philadelphia: Saunders Elsevier; 2010.
  - 6. Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. British Journal of Cancer 2011;105(11):1684-92.
  - 7. Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. Journal of Clinical Oncology 2014;32(10):1066-73.
  - 8. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood 2015;125(1):22-32.
  - 9. Pinter-Brown L, Besa E. Follicular Lymphoma Management Overview. Medscape September 15, 2016:1-26.

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– 10.Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood 2016;127(17):2055-63.

- The following reference has been added to Section 4.2.1:

– 18. Kaplan JB, Gordon LI, Rambaldi A, Gritti G, Popat R, Burris HA, et al. Phase 1 study of TAK-659, an investigational reversible dual SYK/FLT-3 inhibitor, in patients with lymphoma: Updated results from dose-escalation and expansion cohorts. Poster presented at the 59th American Society of Hematology (ASH) Annual Meeting and Expositio. Atlanta, GA, USA; 2017.

Rationale for change: To provide the most current reference citations to support the background information in the protocol.

Change 37. Added a recommendation that prophylaxis for varicella-zoster virus should be administered for all patients in Cohort B.

The primary change occurs in Section 8.8.1 Prophylaxis Against Infection.

Added text: It is recommended that prophylaxis for varicella-zoster virus should be administered for Cohort B [19].

Rationale for change: To follow NCCN guidelines for B-Cell Lymphomas, version 1, 2018.

Change 38. Added a recommendation that the prophylaxis for *Pneumocystis jiroveci* pneumonia should be administered for all patients in Cohort B.

The primary change occurs in Section 8.8.1.2 Prophylaxis for Opportunistic Infections.

Added text: **It is recommended that the prophylaxis for PJP should be implemented in Cohort B regardless of the above-mentioned conditions [19].**

Rationale for change: To follow NCCN guidelines for B-Cell Lymphomas, version 1, 2018.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	15-Nov-2018 20:50 UTC
	Biostatistics Approval	15-Nov-2018 21:13 UTC
	Clinical Approval	15-Nov-2018 22:53 UTC

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