Clinical Study Protocol

NCT Number: NCT04074330

Title: Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma

Study Number: TAK-981-1501

Document Version and Date: Amendment Version 8, 20-May-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma

Sponsor: Takeda Development Center Americas, Inc. (TDC Americas)
95 Hayden Avenue
Lexington, MA 02421

Please note: Takeda Development Center Americas, Inc. (TDC Americas) may be referred to in this protocol as "sponsor" or "Takeda".

Study Number: TAK-981-1501

EudraCT Number: 2020-003946-36

Compound: TAK-981

Date: 20 May 2022 **Amendment Number:** 8

Date	Amendment Number	Region
20 May 2022	Amendment 8	Global
04 October 2021	Amendment 7	Global
02 September 2021	Amendment 6	Global
31 March 2021	Amendment 5	Global
20 January 2021	Amendment 4	Global
18 June 2020	Amendment 3	Global
27 January 2020	Amendment 2	Global
19 July 2019	Amendment 1	Global
04 June 2019	Original protocol	United States and Canada

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.

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

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

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

[redacted], MD Date
[redacted]
(or designee)

[redacted], PhD Date
[redacted]
(or designee)

[redacted], PhD Date
[redacted]
(or designee)

[redacted], RN, MSN Date
[redacted], Oncology Clinical Research
[redacted],
(or designee)

1.3 Protocol Amendment 8 Summary of Changes and Rationale for Amendment

This section describes the changes to the protocol incorporating Amendment 8.

The primary reason for this amendment was to expand Phase 2 enrollment in Cohorts B and C in order to evaluate two dose levels, 120 mg and 60 mg QW. This will add an additional 50 patients to the original Phase 2 (25 patients each to Cohort B and C). This data will be used to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981. New study schematics for Phase 2 of the TAK-981-1501 study are provided in Figure 6.d (Cohort A), Figure 6.e (Cohort B), and Figure 6.f (Cohort C).

Patients enrolled in China will join Phase 2 part of the study, details about China-specific requirements are integrated into this amendment. The major difference between patients enrolled in China and patients enrolled from rest of the world is that selected exploratory assessments are removed for patients enrolled in China, related changes are listed in the following table.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
Expansion of Phase 2 Enrollment in Cohorts B and C			
1	Section 2.0 STUDY SUMMARY, Study Design Section 8.2 Definitions of DLT for Phase 1 Only Section 8.3 Definition of DLT-Evaluable Patients for Phase 1 Only Section 8.5 Dose-Escalation Rules for Phase 1 Only	Removed itemized list of dose-limiting toxicities (DLT) criteria and added reference to the protocol for details. Added "for Phase 1 Only" to the title of Section 8.2, 8.3, and 8.5.	Update
2	Section 4.2.5 Clinical Experience	Updated clinical experience with Phase 1 data to support the Phase 2 design.	Update
3	Section 4.4.1.1 TAK-981, *Rationale for the RP2D of TAK-981 in this Combination Study:*	Updated to provide the rationale for the 2 dose levels, 60 mg and 120 mg once weekly (QW), selected for the Phase 2 Cohorts B and C.	Update
4	Section 2.0 STUDY SUMMARY, Study Design, and Dose Levels (in Phase 1 and Phase 2)	Added text describing that the Phase 2 design will include 2 dose levels of TAK-981 only for Cohorts B and C.	Update

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5	Section 6.3 Phase 2 Study Design Figure 6.b TAK-981-1501: Schedule for TAK-981 Once Weekly and Rituximab Dosing Figure 6.c TAK-981-1501 Study Schematic of Phase 1 and Phase 2 Figure 6.d TAK-981-1501 Study Schematic for Phase 2 Cohort A Figure 6.e TAK-981-1501 Study Schematic for Phase 2 Cohorts B 120 mg and B 60 mg Figure 6.f TAK-981-1501 Study Schematic for Phase 2 Cohorts C 120 mg and C 60 mg	Updated and clarified the overview of the study design in Figure 6.b and Figure 6.c. Added new Figure 6.d, Figure 6.e, and Figure 6.f, for the study design of Cohort A, Cohorts B 120 mg and B 60 mg, and Cohorts C 120 mg, and C 60 mg, respectively.	Clarification
6	Section 2.0 STUDY SUMMARY, Number of Subjects, and Sample Size Justification Section 6.4 Number of Patients and Sites Section 13.3 Determination of Sample Size	Added text noting the addition of approximately 25 patients to each of the 2 new doses within Cohorts B and C. Updated the total number of patients to 180 accordingly.	Update
7	Section 13.3 Determination of Sample Size, *Efficacy-Evaluation Phase (Phase 2)*	Added text to clarify the number of patients for Cohorts B and C considering evaluation of a second dose-level.	Update
Requirements for Patients enrolled in China versus in the Global Study			
8	Section 2.0 STUDY SUMMARY, Study Design Inclusion Criteria, #11 Section 4.4.2.1 Tumor Biopsies Section 6.3 Phase 2 Study Design Section 7.1 Inclusion Criteria, criterion #11 Section 9.4.16.1 Tumor Biopsies (Global Study; Not Applicable to Patients Enrolled in China)	Added text that patients in China will participate only in the Phase 2 part. Updated text to clarify that tumor tissue/archival tissue will not be applicable for patients in China.	Clarification

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9	Section 5.1.3 Additional/Exploratory Objectives Section 5.2.3 Additional/Exploratory Endpoints	Updated section on exploratory objectives and endpoints by the addition of subsections for the global study (excluding patients enrolled in China) and for patients enrolled in China (China-specific).	Clarification
10	Section 9.4.18 Pharmacodynamic Measurements Section 9.4.19 [redacted] Appendix A Schedule of Events, Tables A-1 to A-7	Added wording to clarify parameters collected in the global study (excluding patients in China) or only in patients in China. [redacted]	Clarification
Miscellaneous Clarifications			
11	Section 4.5 Potential Risks and Benefits	Corrected study numbers to read as follows: TAK-981-1502 and TAK-981-1503.	Correction of typographical errors
12	Section 2.0 STUDY SUMMARY Period of Evaluation Section 6.5.2 End of Study/Study Completion Definition and Planned Reporting Section 6.5.4 Total Study Duration	Updated the duration of the entire study.	Clarification
13	Section 2.0 STUDY SUMMARY, Main Criteria for Inclusion (criterion #9) Section 7.1 Inclusion Criteria, Criterion #9.	Deleted the last sentence of Inclusion Criterion #9.	Clarification
14	Section 8.6.3.1 TAK-981 Table 8.a General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs	Added information in the event of QT/corrected QT interval prolongation.	Addition to align with health authority feedback
15	Section 8.6.3.3 COVID-19 Infection	Added sentence to Coronavirus disease 2019 (COVID-19) infection relevant to severe acute respiratory syndrome coronavirus-2 (SARs-CoV2) tests.	Clarification

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16	Section 8.7 Excluded Concomitant Medications and Procedures	Added a parenthetical comment regarding the management of patients for Phase 2.	Clarification
17	Section 9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis	Added a sentence stating that pre-dose samples may be collected within up to 3 days before the visit.	Clarification
18	Section 9.4.19 [redacted]	[redacted].	Clarification
19	Section 13.3 Determination of Sample Size, *Efficacy-Evaluation Phase (Phase 2)*	Added text to last paragraph clarifying that only Phase 2 patients will be included in statistical analysis of efficacy.	Clarification
20	Appendix A Schedule of Events. Table A-1 SOE for Phase 1	Bone marrow biopsy (BMB) was removed at screening; and footnote s was updated to specify BMB at investigator discretion and Lugano guidelines.	Clarification
21	Appendix A Schedule of Events. Table A-2 SOE for Phase 2	Removed all testing on Days 4, 11 and 15, because, for Phase 2, only the QW administration schedule will be used; updated footnote f accordingly.	Clarification
22	Appendix A Schedule of Events [redacted]	Footnote a was modified to add sample collection for patients in the Cohorts B 60 mg and C 60 mg.	Clarification
23	Appendix B Responsibilities of the Investigator, item 10.	Added wording required for record keeping.	Clarification
24	Appendix E Drugs That Interact With the CYP3A Family of CYPs	Added the word "generally" to prohibited.	Clarification
25	Appendix F Examples of Clinical Inhibitors of Pgp	Added the word "generally" to prohibited.	Clarification
26	Appendix G Examples of QTc Interval-Prolonging Agents (Phase 1 Only)	Added clarification.	Clarification

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (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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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. (TDC Americas)	**Compound:** TAK-981
Title of Protocol: Phase 1/2 Study of TAK-981 in Combination With Rituximab in Patients With Relapsed/Refractory CD20-Positive Non-Hodgkin Lymphoma	**EudraCT No.:** 2020-003946-36
Study Number: TAK-981-1501	**Phase:** 1/2

Study Design:

The study consists of 2 phases: Phase 1 (Dose Escalation) and Phase 2 (Expansion in select non-Hodgkin lymphoma [NHL] indications).

The study will consist of a screening period (Day -28 to -1), a treatment period, an end-of-treatment (EOT) visit 30 (+10) days after the last dose occurs when treatment is discontinued for any reason, and a progression-free survival (PFS) follow-up period lasting until disease progression, start of the patient's next line of therapy, or up to a maximum of 12 months for each patient, whichever is soonest, to monitor participants disease progression status. After the occurrence of progressive disease (PD) or start of alternative therapy, patients will continue to have overall survival (OS) follow-up visits that may be performed by phone contact. The OS information will be collected every 12 weeks (±1 week) after the last dose of study drug until death or the conclusion of the study, whichever occurs first.

Day 1 of the study (baseline) will be defined as the first day a patient receives TAK-981. One cycle of treatment will be defined as 21 days. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will receive treatment with TAK-981 and rituximab for up to 12 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the study or study drugs occurs. Treatment may be continued beyond disease progression, with sponsor approval, if, in the opinion of the investigator, the patient continues to experience clinical benefit.

Phase 1: Dose Escalation

The Phase 1 portion of the study consists of dose escalation of TAK-981 in combination with rituximab at a fixed dose in patients with indolent or aggressive relapsed or refractory (r/r) NHL, to identify the maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) and schedule of the combination. PAD can be defined retrospectively once MTD is reached and it can be below MTD or coincide with it (see Section 8.5).

Upon agreement with TAK-981-1501 investigators, and based on the review of the safety data of TAK-981 from the ongoing TAK-981-1002 single-agent study, the selected starting dose of TAK-981 in this study will be 10 mg. (Note, as of Protocol Amendment 6, patients are enrolling into the ≥90 mg twice weekly cohort). TAK-981 will be administered as a 1-hour intravenous (IV) infusion on Days 1 and 8 or Days 1, 4, 8, and 11 in cycles of 21 days. Alternative dosing schedules may be investigated.

Rituximab will be administered on a weekly schedule at 375 mg/m^2 x 3 doses, followed by 375 mg/m^2 on Day 1 of subsequent 21-day cycles for both indolent non-Hodgkin lymphoma (iNHL) and aggressive non-Hodgkin lymphoma (aNHL) patients in cycles of 21 days. Rituximab and TAK-981 will be administered IV until disease progression or unacceptable toxicity.

Dose escalation of TAK-981 will be guided by a Bayesian logistic regression modeling (BLRM) design with overdose control. The recommended Phase 2 dose (RP2D) will be determined from the collective experience in the clinic considering the safety data, preliminary pharmacokinetic (PK) data, preliminary pharmacodynamic data, and any early antitumor activity observed along with the statistical inference from the BLRM.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, except cytokine release syndrome (CRS), which will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS. During the Phase

1 part of the study, dose-limiting toxicity (DLT) was defined as outlined in the protocol.

A Safety Monitoring Committee (SMC) composed of the principal investigators and sponsor clinician will regularly review safety data to ensure patients' safety throughout the Phase 1 portion of the study and make decisions on dose escalation. Dose-escalation decisions will be made based on the DLTs meeting the criteria above that occur during the first 3 weeks of treatment for each patient.

For the first infusion Cycle 1, Day 1 (C1D1) of TAK-981 in combination with rituximab during dose escalation, every patient must be hospitalized for drug administration and observation (for a minimum of 18 hours after the end of TAK-981 infusion). Hospitalization is not required after the first 3 patients at a dose level or expansion of previously cleared dose level, and only if the risk of infusion reactions is considered low based on previous experience. If Grade 3 or greater infusion-related reaction (IRR) or CRS are not observed at PAD or MTD, or if the safety data from the ongoing first-in-human TAK-981-1002 study support the removal of the requirement of hospitalization for the first dose of TAK-981, the decision will be made by the SMC.

Patient enrollment will be staggered between the first and second patients by 72 hours during dose escalation at all dose levels. At each dose level, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through Cycle 1 Day 4 (72 hours) without clinically significant acute toxicities. If more than 3 patients are to be enrolled in a dose level or if de-escalation is indicated, staggering will not be required unless indicated by safety findings.

If infusion reactions or CRS of Grade 2 or greater are not observed at RP2D, the requirement of hospitalization for the first dose will be removed for the Phase 2 study.

Phase 2: Expansion in Select Indications

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with rituximab in patients with select r/r NHL types and indications. The following cohorts will be enrolled:

- Cohort A: r/r diffuse large B-cell lymphoma (DLBCL) progressed or relapsed after chimeric antigen receptor (CAR) T-cell therapy (CAR-T).
- Cohort B: r/r DLBCL progressed or relapsed after 2-3 prior lines of systemic therapy and no prior therapy with CAR T-cells.
- Cohort C: r/r follicular lymphoma (FL) progressed or relapsed after 2-3 prior lines of systemic therapies.

Each cohort will be assessed separately using an adaptive 2-stage design for a single proportion. For Stage 1, each cohort will be analyzed when a prespecified number of patients have been enrolled and had the potential to have at least 1 post-treatment radiologic evaluation of the disease. If the prespecified minimal response rate is not achieved in the first stage for a given cohort, that cohort will be closed to enrollment. However, if a clear clinical benefit has been observed for patients in the cohort (eg, a majority of patients have recorded stable disease at Week 8 and no complete response [CR] or partial response [PR] is recorded) then enrollment into Stage 2 may be allowed for this cohort. If the required response rate during Stage 1 or a good clinical benefit is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients for that cohort has been reached. The final analysis of the primary endpoints for each cohort will take place when all ongoing patients have completed the 6-month disease assessment/survival follow-up.

TAK-981 will be evaluated at a dose of 120 mg once weekly (QW) (the upper dose tested in Phase 1) as well as at the dose of 60 mg QW (a lower yet biologically active dose) in a 21-day cycle, both in combination with a fixed dose of rituximab, in the Phase 2 expansion. The dose cohorts will be: Cohorts B 120 mg/C 120 mg and Cohorts B 60 mg/C 60 mg. This data will be used to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

During Phase 2, an Independent Data Monitoring Committee will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

Patients enrolled in sites in China will participate in Phase 2 of the study.

Primary Objectives:

Phase 1:

- To determine the safety and tolerability of TAK-981 in combination with rituximab in patients with r/r CD20+ NHL.
- To establish the RP2D of TAK-981 in combination with rituximab.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL indications.

Secondary Objectives:

- To characterize the PK profile of TAK-981 in combination with rituximab.

Phase 1:

- To determine the MTD and/or PAD of TAK-981 when administered in combination with rituximab.
- To assess the preliminary antitumor activity of TAK-981-rituximab combination.
- To assess target engagement of TAK-981 (small ubiquitin-like modifier [SUMO]-TAK-981 adduct formation) and SUMOylation pathway inhibition in blood and skin.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL as measured by disease control rate (DCR), duration of response (DOR), time to progression (TTP), and PFS.
- To evaluate the safety and tolerability of TAK-981 in combination with rituximab.

Patient Population: Patients with r/r CD20+ aggressive NHL that have progressed on at least 1 prior regimen, or patients with r/r CD20+ indolent NHL that have progressed on at least 1 prior regimens and are refractory to any anti-CD20 monoclonal antibody.

Number of Subjects: A total of up to approximately 180 patients will be enrolled in the study. Phase 1: Approximately 35 DLT-evaluable patients. Phase 2: Approximately 145 response-evaluable patients.	**Number of Sites:** Estimated total: Approximately 12 sites in Phase 1 and up to a total of approximately 70 sites in the United States, Canada, European Union, Asia, and/or globally.
Dose Levels: Phase 1: TAK-981 at 10, 15, 25, 40, 60, 90, 120, and 160 mg. Intermediate dose levels can be explored in escalation or de-escalation without amending the protocol. Phase 2: • *Cohort A*: 120 mg TAK-981 QW on Days 1 and 8 of each 21-day cycle • *Cohorts B and C, each:* 60 or 120 mg TAK-981 QW on Days 1 and 8 of each 21-day cycle Rituximab: 375 mg/m^2.	**Route of Administration:** TAK-981: IV Rituximab: IV
Duration of Treatment: Patients will continue treatment until any of the discontinuation criteria are met. If no discontinuation criterion is met, patients can continue receiving TAK-981 for 1 year. After 1 year, patients with clinical benefit can continue treatment if approved by the sponsor.	**Period of Evaluation**: Approximately 72 months.

Main Criteria for Inclusion:

1. Adults ≥18 years old.
2. Patient populations:
   a) For Phase 1 Dose Escalation:
      - aNHL including mantle cell lymphoma and DLBCL histologies such as transformed DLBCL from low-grade lymphoma (follicular or others), DLBCL associated with small-cell infiltration in bone marrow, B-cell lymphoma with intermediate features between DLBCL and Burkitt's lymphoma or with intermediate features between DLBCL and Hodgkin lymphoma, FL Grade 3B, and aggressive B-cell lymphoma unclassifiable who must have previously received rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin) and prednisone (R-CHOP) (or equivalent anti-CD20 containing therapy) and 1 additional line of therapy in the r/r setting.
      - iNHL (including FL of Grades 1-3A and marginal zone lymphoma) refractory to rituximab or to any other anti-CD20 monoclonal antibody, who have received at least 1 prior systemic therapy for r/r iNHL:
        – Rituximab or anti-CD20 refractoriness is defined as failure to respond to, or progression during, any previous rituximab/anti–CD20-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab or anti-CD20 dose.

          NOTE: The minimum qualifying rituximab/anti-CD20 dose is 1 full cycle (ie, weekly x 4 doses monotherapy or 1 complete dose if combined with chemotherapy). Prior anti-CD20 antibody or cytotoxic drugs may have been administered as single agents or as components of combination therapies. Each repeated course of the same single agent or combination is considered an independent regimen.

   b) For Phase 2, the following confirmed CD20 positive:
      - r/r DLBCL progressed or relapsed after a prior CAR-T that has received approval by a health authority for the treatment of DLBCL (Cohort A).
      - r/r DLBCL that has progressed or relapsed after at least 2 but no more than 3 prior lines of systemic therapy and has not received prior cellular therapy. At least one prior line of therapy must have included a CD20-targeted therapy (Cohort B).
      - r/r FL that has progressed or relapsed after at least 2 but no more than 3 prior lines of systemic therapy. At least one prior line of therapy must have included a CD20-targeted therapy (Cohort C).
3. Patients must be considered ineligible for, in the opinion of the investigator, or must have refused autologous stem-cell transplantation (ASCT).
4. Eastern Cooperative Oncology Group performance score of ≤2.
5. Adequate bone marrow function per local laboratory reference range at screening as follows:
   - Platelet count ≥75.0 × 10^9/L, Grade 2 thrombocytopenia (platelet count ≥50.0 × 10^9/L) is allowed if it is clearly due to marrow involvement with no evidence of myelodysplastic syndrome or hypoplastic bone marrow if found. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L. Hemoglobin ≥85 g/L (red blood cell transfusion allowed ≥14 days before assessment).
6. Adequate renal and hepatic function, per local laboratory reference range at screening as follows:
   - Calculated creatinine clearance ≥30 mL/min calculated with Cockcroft–Gault formula.
   - Potassium levels ≥ lower limit of normal. For potassium > upper limit of normal (ULN) discussion with Takeda medical monitor/designee recommended.
   - Aspartate aminotransferase and alanine aminotransferase ≤3.0× the ULN of the institution's normal range; bilirubin ≤1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 × ULN, per discussion between the investigator and the medical monitor.
7. Left ventricular ejection fraction ≥40%; as measured by echocardiogram or multiple gated acquisition scan.

8. Suitable venous access for safe drug administration and the study-required PK and pharmacodynamic sampling.
9. Have at least 1 bidimensionally measurable lesion per Lugano Classification (eg, measurable node >1.5 cm in its largest dimension; measureable extranodal lesion >1.0 cm in longest diameter) by computed tomography (CT). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. Willing to consent to 1 mandatory pretreatment and 1 on-treatment skin biopsy during Phase 1. The skin biopsy entry requirement may be discontinued by the sponsor once there is enough pharmacodynamic evidence of target engagement.
11. For patients enrolled in Phase 2, if available, mandatory submission of archival tumor tissue acquired ≤12 months prior to screening. Tumor tissue, including archival tissue, is not applicable to patients enrolled in China.
12. Recovered to Grade 1, baseline or established as sequela, from all toxic effects of previous therapy (except alopecia, neuropathy, autoimmune endocrinopathies with stable endocrine replacement therapy, neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [any of Grade 1, 2, permitted if directly related to bone marrow involvement]).
13. Women of childbearing potential 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 through 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 and 1 additional effective (barrier) method of contraception at the same time, from the time of the signing of the informed consent form through 12 months after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
14. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 12 months after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
15. Subject has provided informed consent.
16. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

Main Criteria for Exclusion:

1. Central nervous system lymphoma; active brain or leptomeningeal metastases, as indicated by positive cytology from lumbar puncture or CT scan/magnetic resonance imaging.
2. Hypersensitivity to TAK-981, rituximab, or any component of the drug product.
3. History of Grade ≥3 IRR that lead to permanent discontinuation of previous rituximab treatment.
4. Previous participation in the TAK-981-1002 clinical study.
5. Posttransplantation lymphoproliferative disease except relapsed NHL after ASCT.
6. Undergone ASCT or treatment with cellular therapy including CAR T within ≤12 weeks of TAK-981 dosing.
7. Prior allogeneic hematopoietic stem-cell transplantation.

8. Lymphomas with leukemic expression.
9. Prior anticancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 5 half-lives before TAK-981 dosing, whichever is shorter. Low dose steroids (oral prednisone or equivalent ≤20 mg per day), hormonal therapy for prostate cancer or breast cancer (in adjuvant situation), and treatment with bisphosphonates and RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitors are allowed.
10. Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.
11. Significant medical diseases or conditions, as assessed by the investigators and sponsor that would substantially increase the risk-benefit ratio of participating in the study. This includes but is not limited to acute myocardial infarction or unstable angina within the last 6 months; uncontrolled diabetes mellitus; significant active bacterial, viral, or fungal infections; severely immunocompromised state; severe non-compensated hypertension and congestive heart failure New York Heart Association Class III or IV; ongoing symptomatic cardiac arrhythmias of >Grade 2, pulmonary embolism, or symptomatic cerebrovascular events; or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). Chronic atrial fibrillation on stable anticoagulant therapy is allowed.
12. Known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to immunoglobulin therapy) for chronic hepatitis B. Known HIV infection.
13. Second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy as defined in Exclusion Criterion 9.
14. Receipt of any live vaccine within 4 weeks of initiation of study treatment.
15. Active, uncontrolled autoimmune disease requiring >20 mg of prednisone or equivalent, cytotoxics, or biologicals.
16. Corticosteroid use within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. Patients requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for lymphoma control or white blood cell count lowering are not eligible.
17. History of medical or psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent.
18. Patients with baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, >470 ms for women and >450 ms for men and a history of congenital long QT syndrome or torsades de pointes).
19. Receiving or requiring the continued use of medications that are known to be strong or moderate inhibitors and inducers of cytochrome P-450 (CYP)3A4/5 and strong P-glycoprotein (Pgp) inhibitors. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and Pgp inhibitors) before receiving a dose of TAK-981.
20. Female patients who are lactating and breastfeeding or have a positive urine or serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
21. Patients in Germany who are committed to an institution by virtue of an order issued either by judicial or administrative authorities as required by German law.

Main Criteria for Evaluation and Analyses:

The primary endpoints are:

Phase 1:

- Frequency, severity, and duration of treatment-emergent adverse event (TEAEs) and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS.
- Occurrence of DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- Overall response rate (ORR) (CR + PR) as defined by the investigator according to Lugano Classification for lymphomas.

Secondary endpoints for this study are:

- PK parameters after the first dose of TAK-981 on C1D1 and C1D8 (data permitting):
  - Maximum observed plasma concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the plasma concentration-time curve from time 0 to time t.
  - Area under the plasma concentration-time curve from time 0 to infinity.
  - Terminal disposition phase half-life.
  - Total clearance after IV administration.
  - Volume of distribution at steady state after IV administration.

Phase 1:

- ORR, DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in skin/blood.

Phase 2:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS.
- DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.

Statistical Considerations:

In Phase 1, only TAK-981 will be escalated. Dose escalation of TAK 981 will be cohort-based with an adaptive Bayesian logistic regression modeling (BLRM) guided by escalation with overdose control principle that is based on the posterior probability of having a DLT. The final decision on escalating to the next dose level will be taken jointly by the sponsor and the participating investigators according to the BLRM along with safety, clinical, PK, and pharmacodynamic data.

In Phase 2, the primary endpoint is ORR (CR + PR) as assessed by the investigator according to Lugano criteria for patients with lymphoma. The sample sizes for disease-specific patient populations will be estimated using an adaptive design based on Simon's 2-stage design for a single proportion with the different hypotheses assumptions of ORR for disease-specific cohorts.

Sample Size Justification:

It is anticipated that up to approximately 180 patients will be enrolled in this study, including the dose-escalation phase (approximately 35 patients), and the 5 expansion dose cohorts for Phase 2 (up to approximately 145 response-evaluable patients) to evaluate efficacy in patients with select lymphoma.

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 supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator

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

3.3 List of Abbreviations

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
ANC	absolute neutrophil count
aNHL	aggressive Non-Hodgkin Lymphoma
ASCT	autologous stem-cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to time t
BCRP	breast cancer resistance protein
BIW	twice weekly
BLRM	Bayesian logistic regression modeling
BSA	body surface area
C1D1	Cycle 1, Day 1
C1D2	Cycle 1, Day 2
C1D8	Cycle 1, Day 8
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T cell therapy
CL	total clearance after intravenous administration
COVID-19	coronavirus disease 2019
CNS	central nervous system
C_{max}	maximum observed plasma concentration
CR	complete response
CRA	cytokine release assay
CRS	cytokine release syndrome
CT	computed tomography
CYP	cytochrome P-450
DC	dendritic cells
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
FDA	Food and Drug Administration
FDG-PET	^{18}fluorodeoxyglucose positron emission tomography

FIH	first-in-human
FL	follicular lymphoma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobulin
IL	interleukins
iNHL	indolent non-Hodgkin lymphoma
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IV	intravenous
LVEF	left ventricular ejection fraction
MCP-1	monocyte chemotactic protein-1
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
Pgp	P-glycoprotein
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan

PR	partial response
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
QW	once weekly
R-CHOP	rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin) and prednisone
RANKL	receptor activator of nuclear factor kappa-B ligand
RANTES	regulated upon activation normal T-cell expressed and secreted
RBC	red blood cell
RP2D	recommended Phase 2 dose
r/r	relapsed or refractory
SAE	serious adverse event
SMC	Safety Monitoring Committee
SOE	schedule of events
STAT	within 1-hour immediately
SUMO	small ubiquitin-like modifier
SUMO1	small ubiquitin-like modifier 1
SUMO2	small ubiquitin-like modifier 2
SUMO3	small ubiquitin-like modifier 3
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse events
TLS	tumor lysis syndrome
t_{max}	time of first occurrence of C_{max}
TTP	time to progression
ULN	upper limit of normal
Vss	volume of distribution at steady state after intravenous administration

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is among the most common cancers in the United States and Europe with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay et al. 2018; Siegel et al. 2018). NHL is a heterogeneous group of malignancies with varying clinical characteristics that are optimally managed through a range of different treatment modalities. The spectrum of NHL includes more indolent variants such as follicular lymphoma (FL) and marginal zone lymphomas, to more aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL). While systemic chemotherapy is a mainstay of treatment for most NHL variants, antitumor directed monoclonal antibodies have an important role in the treatment of this disease (Oflazoglu and Audoly 2010). Monoclonal antibodies such as rituximab, which targets the B-cell antigen CD20, are now part of the standard treatment regimens for many B-cell NHLs (Keating 2010). However, once NHL becomes refractory to standard chemotherapy and antibody-based therapies, the overall prognosis is poor, with limited long-term survival. Thus, novel and effective therapies are needed to address this high unmet medical need.

This study will explore clinical proof of concept of the combination of TAK-981 with rituximab to treat FL and DLBCL.

4.1.1 Follicular Lymphoma

Indolent NHL (iNHL) represents 40% of all NHL subtypes, with FL occurring with the greatest frequency (Harris et al. 1999). iNHL presents with a broad spectrum of disease characteristics. Patients with FL often experience a chronic relapsing and remitting disease course and are exposed to several successive treatment regimens, resulting eventually in death due to disease progression. In general, treatment is reserved for patients who develop significant symptoms or who are sufficiently high-risk to merit early therapy (Gribben 2007). The most common frontline therapies include a combination of alkylators (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or bendamustine) in combination with the anti-CD20 monoclonal antibody rituximab. In addition, single-agent rituximab is also often administered as frontline therapy, particularly in patients with lower disease burden or who may not tolerate combination chemo-immunotherapy (Sousou and Friedberg 2010). Rituximab was originally approved for use in patients with relapsed and refractory FL and low-grade lymphoma.

For patients with FL who initially respond (complete response [CR] or partial response [PR]) with a time to progression (TTP) of at least 6 months and then experience relapse after single-agent rituximab, retreatment with either rituximab alone or in combination with chemotherapy is frequently given (Gribben 2007; Kahl et al. 2014; National Comprehensive Cancer Network 2019). Patients who become refractory to rituximab alone or in combination with chemotherapy have limited options for effective treatment. In the third line setting, treatment with phosphoinositide-3 kinase delta inhibitors are available but are associated with significant toxicities (Gopal et al. 2014).

4.1.2 Diffuse Large B-Cell Lymphoma

Aggressive non-Hodgkin Lymphoma (aNHL) accounts for approximately 30% to 40% of all NHL (The Non-Hodgkin's Lymphoma Classification Project 1997) and DLBCL is the most common histological subtype (Beham-Schmid 2017). Combination chemotherapy with the addition of rituximab is standard of care for patients with newly diagnosed DLBCL. However, approximately 40% of patients with DLBCL relapse following initial immunochemotherapy (Vaidya and Witzig 2014). For eligible patients, high-dose chemotherapy, including salvage regimens such as rituximab, ifosfamide, carboplatin, etoposide (R-ICE), and autologous stem-cell transplantation (ASCT) are the treatments of choice for some patients with relapsed disease. For patients with disease relapse following ASCT, cell therapy with autologous chimeric antigen receptor (CAR) T-cell targeti ng CD19 has emerged as an option, however with significant toxicity including cytokine release syndrome (CRS) and neurotoxicity (Neelapu et al. 2017; Schuster et al. 2019).

While various salvage regimens comprising combination chemotherapy are available for relapsed/refractory disease, no standard salvage regimen exists currently. An international, multicohort retrospective research study evaluated outcomes in relapsed or refractory (r/r) DLBCL (Crump et al. 2017). The overall response rate (ORR) was 26% to the next line therapy (rituximab containing polychemotherapy regimens), and the median overall survival (OS) was 6.3 months. Apart from anti-CD20 monoclonal antibodies, the development of new therapies for r/r NHL has been limited to immune checkpoint inhibitors in primary mediastinal B-cell lymphoma (Armand et al. 2018), and ibrutinib and lenalidomide in mantle cell lymphoma (Witzig et al. 2017), both low prevalent diseases. Therefore, there remains an unmet need for patients with DLBCL that relapse following cellular therapy and for those have relapsed or who are not responsive to anti-CD20 treatment regimens. The development of more effective treatments for relapsed/refractory DLBCL represents a high unmet medical need.

4.2 TAK-981

TAK-981 is a first in class small molecule inhibitor of small ubiquitin-like modifier (SUMO)ylation.

4.2.1 Protein SUMOylation Biology in Cancer

SUMOylation is a post-translational modification that attaches a SUMO protein to protein substrates, regulating their activity, subcellular localization and stability (Geiss-Friedlander and Melchior 2007). There are 3 functional mammalian paralogues of the SUMO proteins, small ubiquitin-like modifier 1 (SUMO1), small ubiquitin-like modifier 2 (SUMO2), and small ubiquitin-like modifier 3 (SUMO3) (Gareau and Lima 2010; Geiss-Friedlander and Melchior 2007), which are attached to their substrate proteins as monomers (SUMO1) or poly SUMO chains (SUMO2, SUMO3). The SUMOylation process is mediated by an enzymatic cascade similar to that described for ubiquitination (Geiss-Friedlander and Melchior 2007; Seeler and Dejean 2017). An E1 activating enzyme consisting of an SUMO-activating enzyme subunit 1/SUMO-activating enzyme subunit 2 heterodimer binds SUMO, generating a SUMO-SUMO-activating enzyme subunit 2 thioester that is transferred to SUMO-conjugating enzyme (UBC9), the sole E2 conjugating enzyme in the pathway, following which SUMO is then covalently attached to a lysine

residue on target proteins by an E3 ligase. TAK-981 interrupts this cascade by forming an irreversible covalent adduct with SUMO, preventing its transfer from SUMO-activating enzyme to UBC9.

SUMOylation has been reported to regulate cellular processes important for tumor cell proliferation and survival (He et al. 2017; Seeler and Dejean 2017). In addition, SUMOylation has also been shown to play a key role in regulating innate immune responses. A net inhibitory effect of SUMOylation on type 1 interferon (IFN) expression has been demonstrated (Decque et al. 2016), such that inhibiting SUMOylation by genetic means resulted in enhanced basal expression levels and sensitization of induction of type 1 IFNs, promoting enhanced innate immune responses to pathogenic stimuli. The pattern recognition receptor pathway, upstream of the transcription factors which promote expression of type I IFNs, has been shown to play a key role in the body's tumor surveillance mechanism, activating innate immune responses that can bridge to an adaptive antitumor response (Woo et al. 2014). Production of type 1 IFNs promotes maturation of dendritic cells (DCs) and cross presentation of tumor antigens to naïve T-cells eliciting cytotoxic T-cells and thereby propagating an adaptive antitumor response. Central to the mechanism of action of TAK-981 is production of type 1 IFNs and induction of an innate immune response with activation of both natural killer (NK) cells and macrophages.

Initiation of a type 1 IFN response represents a strategy for modulating the cancer immunity cycle at its inception, differentiated from the currently approved immuno-oncology therapies, the immune checkpoint inhibitors, which function to disinhibit cytotoxic T-cell activity at more distal parts of the cycle (Chen and Mellman 2013). The full potential of leveraging type 1 IFN responses to stimulate antitumor immunity has yet to be realized. Direct systemic administration of IFNα is hampered by serious clinical toxicity. Alternative strategies to induce type 1 IFN by stimulating the pattern recognition receptor pathway through administration of agonists (such as stimulator of IFN genes protein or toll-like receptor agonists) have been largely limited to delivery by intratumoral injection, or topical application, indicative of toxicities associated with systemic administration (Adams 2009). Inhibition of SUMOylation represents a novel therapeutic strategy for initiating type 1 IFN responses and promoting antitumor immune responses.

Brief summaries of nonclinical pharmacology, pharmacokinetic (PK), and toxicity studies are provided below. More detailed information is provided in the IB.

4.2.2 Nonclinical Pharmacology

Biochemical assays demonstrated that TAK-981 is a mechanism-based inhibitor of SUMO-activating enzyme that potently inhibits enzyme activity by forming a covalent adduct with SUMO. Strong selectivity for SUMO-activating enzyme was observed over the other closely related ubiquitin-activating enzymes ubiquitin-activating enzyme, Nedd8-activating enzyme, and autophagy related 7 enzyme. Selective and potent inhibition of SUMO-activating enzyme and SUMOylation by TAK-981 was also demonstrated in cultured mouse and human tumor cell lines and the antiproliferative activity of TAK-981 was determined in a panel of 7 mouse hematologic and solid tumor cell lines. In ex vivo assays evaluating the activity of TAK-981 on the function of human monocyte derived macrophages and human NK cells (both derived from peripheral blood

mononuclear cells), TAK-981 increased the phagocytic activity of monocyte derived macrophages and increased the cytotoxicity of NK cells in both the absence and presence of the anti-CD20 antibody rituximab. In addition, TAK-981 upregulated inflammatory markers on macrophages (CD80, CD86) and the activation marker CD69 and degranulation marker CD107 on NK cells. These activities were dependent on type 1 IFN signaling, demonstrating that TAK-981-mediated SUMO-activating enzyme inhibition leads to the functional activation of human macrophages and human NK cells via type 1 IFN signaling ex vivo. In a mouse model bearing the human OCI-Ly10 DLBCL tumor xenograft, TAK-981 demonstrated target engagement (formation of the TAK-981-SUMO adduct) and pathway inhibition, inducing robust, durable, and dose-responsive inhibition of SUMO2/SUMO3 conjugates in tumor cells. Significant antitumor activity was demonstrated against OCI-Ly10 xenografts in severe combined immunodeficiency mice (lacking B and T cells, but with intact innate immune response) following administration of single-agent TAK-981 or the anti-CD20 antibody rituximab. Combination of TAK-981 with rituximab resulted in CRs, defined as absence of palpable tumors, in every tumor-bearing mouse treated with the combination. The ability of TAK-981 to promote activation of macrophages and NK cells, key innate effector cells which mediate the activity of anti-tumor antibodies such as rituximab, suggests that enhancement of antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cell-mediated phagocytosis (ADCP) may provide a mechanistic rationale for this synergistic combination activity.

Ex vivo characterization of mouse bone marrow-derived DCs and human DCs isolated from peripheral blood mononuclear cells demonstrated that TAK-981 promoted DC maturation as assessed by upregulation of the T cell co-stimulatory markers CD40, CD80, and CD86. Consistent with these findings, TAK-981 also induced release of type 1 IFNs and pro-inflammatory chemokines from human DCs in vitro. Antitumor activity of TAK-981 was demonstrated in fully immune-competent BALB/c mice bearing syngeneic A20 lymphoma tumors. CRs were achieved most frequently after treatment with 7.5 mg/kg TAK-981 twice weekly (BIW) but also after treatment with 15 mg/kg TAK-981 once weekly (QW). Re-challenge of mice that had achieved CRs with either the same (A20) or a different (CT26, colorectal) tumor type demonstrated protection from A20, but not CT26, tumor growth, indicative of a protective antitumor immune response in mice with CRs. TAK-981 treatment of B and T cell-deficient BALB/c Rag2 knockout mice bearing A20 lymphoma isografts resulted in diminished tumor growth inhibition compared to treatment in wild type BALB/c mice and CR was not achieved, demonstrating dependency of TAK-981 antitumor activity on lymphocytes. Treatment of the tumor-bearing Rag2 knockout mice with the type 1 IFN receptor IFNAR1 neutralizing antibody before administration of TAK-981 resulted in a marked decrease in TAK-981 antitumor activity, indicative of a key role for type I IFN signaling in the antitumor mechanism of action of TAK-981.

A pharmacodynamic study assessing the response of lymphocyte populations in circulation and in lymphoid organs after TAK-981 administration to immune-competent BALB/c mice demonstrated marked, moderate, and trending toward depletion of B lymphocytes in the blood, spleen, and bone marrow respectively. T lymphocyte numbers were also decreased in the blood within 24 hours of treatment, but showed a clear trend towards increased numbers in the lymph

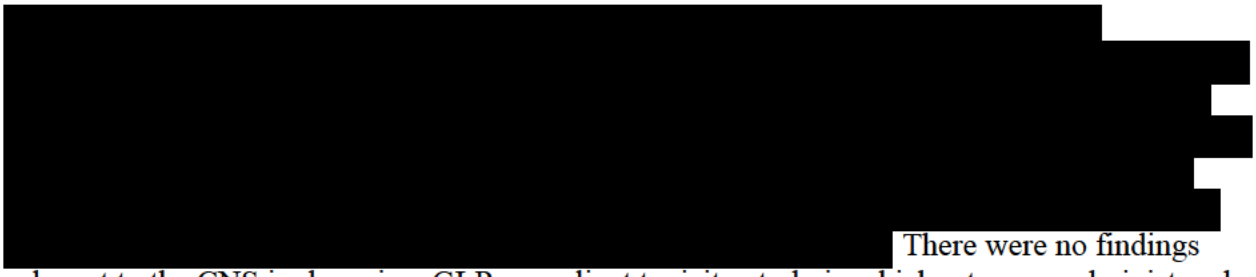
nodes, suggestive of a TAK-981-mediated T cell redistribution from the periphery to the lymph nodes.

In an in vitro competitive binding screen, TAK-981 inhibited ligand binding to adrenergic α1, α2, and β2 receptors, dopamine D2L, D2S, and D3 receptors, dopamine transporter, serotonin 5-HT1A, 5-HT2A, and 5-HT2B receptors, adenosine transporter, and phosphodiesterase 5 and 6. The 50% inhibitory concentration (IC_{50}) values for inhibition of ligand binding to the adrenergic α1B, adrenergic α1D, adrenergic α2C, dopamine D2L, dopamine D3, and serotonin 5-HT2B receptors are 4.68, 0.32, 8.82, 1.53, 1.76, and 1.87 μM, respectively. In addition, the IC_{50} for inhibition of dopamine uptake is 4.9 μM. In the Phase 1 clinical trial, TAK-981-1002, the highest maximum observed plasma concentration (C_{max}) observed after 1 cycle of 120 mg BIW was 2.99 μM. Given the high protein binding of TAK-981 in human plasma, it is unlikely that TAK-981 will bind and modulate these receptors at clinically relevant concentrations. Modulation of these receptors is readily monitorable (eg, altered blood pressure, heart rate, gastrointestinal motility, and mood/behavior) in humans. Inhibition of ligand binding to dopamine receptors and dopamine transporter can be associated with alterations in mood/behavior in humans. While a biodistribution study has not been performed, TAK-981 is not predicted to cross the blood brain barrier.

In vitro cardiovascular assessment revealed minimal inhibition of hERG and hCav1.2 at 10 μM (17.2% and 17.5%, respectively). In a stem cell-derived cardiomyocyte in vitro assay, TAK-981 had minimal effects on cell index, beat ratio, and beat frequency and there was no evidence of arrhythmic activity; effects on twitch amplitude were not considered to be biologically meaningful. In vivo cardiovascular assessment in beagle dogs revealed dose-related increases in heart rate and body temperature from approximately 6 to 24 hours postdose. These findings were not associated with changes in blood pressure or in electrocardiogram (ECG) traces. Based on the currently available nonclinical information, TAK-981 may result in monitorable effects on the cardiovascular system (increased heart rate) that may be related to increased body temperature. In vitro and in vivo cardiovascular assessment indicate that the risk of QT prolongation in humans is low.

Safety pharmacology endpoints relevant to the respiratory system and central nervous system (CNS) were assessed in vivo in rats and dogs. There were no significant findings relevant to the respiratory system and CNS at tolerated exposures in either species. However, in a non-Good Laboratory Practice (GLP)-compliant study in rats, interstitial lung inflammation was observed at ≥5 mg/kg when TAK-981 was administered daily for 3 or 7 days. This microscopic finding had no clinical observation correlate and was not present in GLP-compliant studies in rats in which TAK-981 was administered on a weekly schedule for 5 doses or a BIW schedule for 4 doses.

[redacted]



There were no findings relevant to the CNS in dogs; in a GLP-compliant toxicity study in which rats were administered TAK-981 BIW for 4 doses, functional observational battery revealed moderately decreased ambulatory and total movements in males on Day 4.

4.2.3 Nonclinical PK

TAK-981 has an acceptable nonclinical PK profile for continuing evaluation and development in humans.

- In plasma after single intravenous (IV) administration, TAK-981 showed moderate to high plasma clearance and volume of distribution at steady state (V_{ss}) after IV administration in mice, rats, dogs, and monkeys. In blood after a single IV administration, TAK-981 showed low blood clearance and V_{ss} in mice, rats, dogs, and monkeys.
- There were no pronounced sex-related differences in plasma exposure to TAK-981 in repeat-dose IV studies in rats or dogs.
- In rats and monkeys TAK-981 urinary excretion is not considered a major route of clearance, suggesting metabolism is a major elimination pathway.
- TAK-981 was highly bound to protein in mouse, rat, dog, and human plasma and whole blood at 5 and 50 µM (≥92.1%). TAK-981 was also extensively partitioned into the red blood cells (RBCs) of mice, rats, dogs, monkeys, and humans.
- In vitro metabolism studies indicated that TAK-981 had medium clearance in dogs and high clearance in mouse, rat, monkey, and human S9 fractions. TAK-981 had moderate clearance in rat, dog, monkey, and human hepatocytes. The major metabolic pathways of TAK-981 was oxidation and oxidation followed by glucuronidation. No unique human metabolites were identified in the in vitro evaluation. Cytochrome P-450 (CYP)3A4/5 and aldehyde oxidase were the major contributors to the metabolism of TAK-981 with 70% to 76% and 19.1% contribution, respectively. No other CYP contributed >4% individually.
- The potential risk for TAK-981 to induce CYP1A2, 2B6, and 3A4 activities is very low.
- TAK-981 is a reversible inhibitor of some of CYPs with IC_{50} values for inhibition of 37.1 (CYP1A2), 21.6 (CYP2B6), 57.2 (CYP2C8), 18.7 (CYP2C9), 7.9 (CYP2C19), 7.1 (CYP2D6), 79.9 (CYP3A4/5; midazolam), and 7.9µM (CYP3A4/5; testosterone). Clinically significant drug-drug interaction with CYP2D6, 2C19, or 3A4/5 substrates is expected to be low with a 1-hour infusion of 182 mg TAK-981 with a simulated C_{max} of 0.702 µM based on

physiologically based PK simulations. However, there is drug-drug interaction potential with CYP3A4/5 inhibitors or inducers with TAK-981 as a victim.

- TAK-981 is a substrate of P-glycoprotein (Pgp) but not of breast cancer resistance protein (BCRP) and is an inhibitor of Pgp (IC_{50} of 30.4 μM) and BCRP (IC_{50} of 24.4 μM). The drug-drug interaction potential with Pgp and BCRP substrates with TAK-981 as a perpetrator is low; however, there is a drug-drug interaction potential with Pgp inhibitors or inducers with TAK-981 as a victim.
- Allometric scaling was used to project human PK parameters based on PK parameters from rats, dogs, and monkeys. For a 70-kg human, the projected plasma clearance was moderate (0.62 L/h/kg), with a V_{ss} of 4.04 L/kg, volume of distribution during the terminal disposition phase of 6.51 L/kg, and a half-life of 7.3 hours.

4.2.4 Nonclinical Toxicology

The nonclinical toxicology profile of TAK-981 has been fully characterized in a comprehensive toxicology program that included single- and repeat-dose studies in rats and dogs. Repeat daily dosing resulted in unacceptable toxicity due to multiorgan failure in rats and fever (increased body temperature) in dogs. Increased body temperature was observed in dogs after a single dose of TAK-981 at ≥3 mg/kg and was dose-limiting at 12 mg/kg with body temperature reaching up to 40.3ºC (compared to baseline body temperature of 37.8ºC to 38.9ºC). Increased body temperature (0.5°C to 2.0°C) was also observed in dogs at ≥3 mg/kg in a single-dose cardiovascular assessment study and after repeat once daily or QW dosing. Increased body temperature in the cardiovascular assessment study was not associated with effects on blood pressure or ECG morphology but was associated with increased heart rate. Because intermittent dosing on a QW or BIW schedule was demonstrated to be efficacious in mouse models, both QW and BIW schedules were examined in GLP toxicology studies. QW dosing (5 doses) was associated with multiorgan failure in rats at ≥20 mg/kg, but was well-tolerated in dogs up to the top dose of 6 mg/kg. BIW dosing (4 doses) was well-tolerated in both species up to the top dose of 10 mg/kg in rats and 4 mg/kg in dogs; therefore, in the Phase 1 study TAK-981-1002, patients were dosed with TAK-981 on either the QW (2 weeks on and 1 week off) or the BIW schedule.

The primary toxicity with BIW dosing was dose-dependent mild to marked decreases in peripheral blood lymphocyte counts that affected T cells, T-cell subsets (helper, cytotoxic, activated, memory, regulatory), B cells, and NK cells approximately equally. Decreases in lymphocyte count were associated with decreases in lymphoid cellularity in the primary and secondary lymphoid organs including the thymus, spleen, lymph nodes, and gut-associated lymphoid tissue. Decreases in other circulating cell types including neutrophils, monocytes, basophils, and/or eosinophils were also observed, but were of decreased severity compared to decreases in lymphocyte counts. Additional effects observed with BIW dosing were limited to myeloid hyperplasia in the bone marrow in rats at 10 mg/kg and in dogs at 4 mg/kg; modest increases in serum monocyte chemotactic protein-1 (MCP-1), IP-10 (rats only), and regulated upon activation normal T-cell expressed and secreted (RANTES) (rats only) at ≥0.5 mg/kg (with no increases in cytokines typically associated with CRS); injection site reactions in rats at ≥0.5 mg/kg; single cell necrosis in the stomach in dogs at

≥2 mg/kg; and renal pelvis inflammation and fibrinoid vascular necrosis (without involvement of the renal parenchyma or alterations in renal parameters) in dogs at 4 mg/kg. Additional TAK-981-related effects after repeat daily or QW dosing, often at non-tolerated doses only, were observed in the bone marrow, liver, kidney, urinary bladder (dog only), gastrointestinal tract, heart, musculoskeletal system, lung (rat only), endocrine system (rat only), glandular organs (rat only), and reproductive tract (rat only). All target organ toxicities at tolerated doses were considered to be monitorable, except for inflammation and vascular necrosis in the renal pelvis in dogs. All target organ toxicities were completely or partially reversible.

An in vitro cytokine release assay (CRA) was performed to evaluate the risk of TAK-981 to produce clinically significant CRS. TAK-981 was incubated with human whole blood (n = 10) at up to 20 μM for 24 hours. There were no effects on IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12(p70), tumor necrosis factor-alpha, IFNγ, or granulocyte colony stimulating factor levels. TAK-981-related increases in IP-10 levels were noted at ≥0.5 μM (8- to 50-fold compared to negative control). Increases were dose-dependent from 0.5 to 5.0 μM, while increases at >5 μM were not dose-dependent. TAK-981–related effects were limited to moderate increases in IP-10 at ≥0.5 μM. Based on these results, this CRA can be considered negative. TAK-981 was not mutagenic in a GLP-compliant Ames assay; however, it was associated with genotoxicity at ≥5 mg/kg in an in vivo micronucleus assay in rats, and was clastogenic in an in vitro chromosomal aberration assay with human peripheral blood lymphocytes. Reproductive and developmental toxicity studies have not been conducted. There were no TAK-981–related reproductive findings in rats or dogs with BIW dosing or in dogs with QW dosing. In the rat study with QW dosing, there were partially to fully reversible microscopic findings in reproductive tissues. In a non-GLP compliant, 7-day repeat-dose toxicity study in male rats, there were microscopic and organ weight effects in reproductive tissues in animals that had significant systemic toxicity. TAK-981 did not demonstrate phototoxic potential in an in vitro assay.

4.2.5 Clinical Experience

TAK-981 is currently being evaluated in this ongoing Phase 1/2 clinical efficacy and safety study of the combination with rituximab in patients with relapsed/refractory indolent or aggressive CD20+ NHLs (Study TAK-981-1501), in the ongoing first-in-human (FIH) Phase 1/2 study in patients with advanced or refractory solid tumors or relapsed/refractory hematologic malignancies (Study TAK-981-1002), in one ongoing Phase 1b/2 clinical efficacy and safety study of the combination with pembrolizumab in patients with advanced or metastatic solid tumors (Study TAK-981-1502), and in one ongoing Phase 1b/2 safety and efficacy study of the combination with monoclonal antibodies in patients with relapsed and/or refractory multiple myeloma (Study TAK-981-1503).

As of the 28 June 2021 data cutoff for the IB, 135 patients were treated with TAK-981 across 4 clinical trials; 81 patients received TAK-981 as a single agent, and 54 patients received TAK-981 as part of a combination regimen. Overall, TAK-981 has been well-tolerated, with treatment-emergent adverse events (TEAEs) consistent with induction of IFN signaling or with the patients' underlying cancer disease (see Section 4.5.1 and Section 8.10 for more details). The most common TEAEs (>20%) in the total population in Studies TAK-981-1002, TAK-981-1501, and

TAK-981-1502 included fatigue, pyrexia, nausea, diarrhea, chills, and headache (Table 4.a). Overall, preliminary efficacy is being observed, and efficacy evaluations are ongoing. (Refer to current TAK-981 IB for details).

Table 4.a TAK-981 (All Clinical Studies): Most Frequent (≥10% of All Patients) TEAEs

Preferred Term	Number of Patients (%) Total (N = 135)
Fatigue	49 (36.3)
Pyrexia	46 (34.1)
Nausea	45 (33.3)
Diarrhea	39 (28.9)
Chills	36 (26.7)
Headache	35 (25.9)
Vomiting	27 (20.0)
Decreased appetite	26 (19.3)
Dyspnea	22 (16.3)
Abdominal pain	21 (15.6)
Hypokalemia	21 (15.6)
Anemia	19 (14.1)
Oedema peripheral	17 (12.6)
Constipation	14 (10.4)

Source: Investigator's Brochure Edition 4, data cut-off date: 28 June 2021, Table 5.g.
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events;
TEAE: treatment-emergent adverse event.
Adverse events graded according to NCI CTCAE Version 5.0.

The TAK-981 studies reported some pharmacologically active dose (PAD) at ≥60 mg. In study TAK-981-1002, pharmacodynamic activity, including SUMO pathway inhibition and activation of IFN-I signaling, was most consistently detected at doses ≥60 mg. The maximum tolerated dose (MTD) was determined to be 120 mg; the recommended Phase 2 dose (RP2D) for single-agent TAK-981 was 90 mg, when administered BIW (Days 1, 4, 8, and 11) in a 21-day cycle. Out of the 81 patients, 4 dose-limiting toxicities (DLTs) were reported in the single-agent study: transient Grade 3 serum alanine aminotransferase and aspartate aminotransferase elevations at 60 mg BIW; Grade 3 recurrent pneumonitis after a previous pneumonitis with an anti–PD-1 inhibitor at 90 mg BIW, and 2 DLTs at 120 mg BIW; transient Grade 3 stomatitis; and transient Grade 3 cognitive disturbance with Grade 2 lethargy. The most common (≥20%) TEAEs in Study TAK-981-1002 across 10 dose levels (3 mg to 120 mg) and 3 dosing schedules (Days 1, 4, 8, and 11; Days 1 and 8; and Days 1, 8, and 15 in a 21-day cycle) were fatigue, nausea, headache, diarrhea, pyrexia, dyspnea, vomiting, and decreased appetite. Reversible CRS was reported in 9 patients with 5 patients experiencing Grade 1 events (Grade 1 or 2 fever only) and 4 patients experiencing Grade 2 events (ie, fever and low peripheral oxygen saturation or low blood pressure). Grade 2 CRS was managed symptomatically (eg, oral antipyretics for fever, in addition to oxygen for hypoxia or IV

fluids for low blood pressure). No patient with CRS required vasoactive drug support or anti-IL-6 directed therapies.

The preliminary analysis of available corrected QT interval (QTc) data is consistent with a low risk of QTc prolongation after IV administration of TAK-981 alone at doses of 3 to 120 mg (Study TAK-981-1002) or in combination with rituximab at doses of 10 to 120 mg (Study TAK-981-1501). A separate QTc report is on file with the sponsor.

In Phase 1 of this study, TAK-981-1501, patients were treated in cohorts with increasing doses of TAK-981 (10, 40, 60, 90, and 120 weekly [QW, Days 1 and 8]), with fixed doses of rituximab (375 mg/m^2 [QW Days 1, 8, 15 during Cycle 1 and on Day 1 of each subsequent cycle]). One alternative schedule of TAK-981 was implemented, as allowed per protocol; this was a 90 mg twice weekly (BIW) cohort where TAK-981 was administered on Days 1, 4, 8, and 11, with rituximab administered as described above. Cycle duration in all cohorts was 21 days. As of 07 Feb 2022, a total of 31 patients with relapsed/refractory CD20-positive NHL were enrolled in this study. Pharmacodynamic activity, including SUMO pathway inhibition and activation of IFN-I signaling, was most consistently detected at doses ≥60 mg and up to the dose level of 120 mg. PK/pharmacodynamics relationship modeling showed dose-dependent target engagement that begins to plateau approximately at the 60 mg dose of TAK-981, and a near maximal effect in terms of Type 1 IFN effector cell activation at the 120 mg dose of TAK-981.

In this study, TAK-981-1501, combining TAK-981 with rituximab, as of the data cut-off of 07 Feb 2022, no DLTs were reported, an MTD was not identified, and dose modifications have been infrequent and similar across the QW Phase 1 dose cohorts. The most common (≥20%) TEAEs in Study TAK-981-1501 across 5 dose levels (10 mg to 120 mg) and 2 dosing schedules (Days 1 and 8; and Days 1, 4, 8, and 11, both in 21-day cycles) were fever, chills, diarrhea, fatigue, headache, hypokalemia, and nausea. These TEAEs could be characterized as transient flu-like symptoms temporally associated to TAK-981 administration and consistent with induction of IFN signaling. CRS (Grade 1) was reported in 1 patient in the 120 mg QW cohort who complained of fever and chills; no anti-IL-6 directed therapy was needed. Rates of TEAE, including TAK-981 related TEAEs, Grade ≥3 adverse events (AEs), and SAEs, were generally similar across QW dosing cohorts ≥60 mg. In this Phase 1 study, safety was the primary endpoint while efficacy was predominantly signal seeking, as such a heterogeneous patient population, ie patients with various subtypes of aggressive and indolent non-Hodgkin's lymphoma, were enrolled. As of the data cutoff date, 7 patients out of 26 response evaluable patients have achieved an objective response (2 CRs and 5 PRs). These objective responses were investigator-assessed and occurred in patients across the dose cohorts and across NHL disease subtypes.

Overall, TAK-981 was well-tolerated. The majority of the observed AEs were consistent with the patients' underlying cancer disease and/or IFN signaling. Refer to the TAK-981 IB for additional details.

4.3 Rituximab

Rituximab is a chimeric murine/human immunoglobulin (Ig) G1 kappa monoclonal antibody that targets CD20. Its mechanisms of actions are thought to be ADCC, complement-dependent

cytotoxicity, and induction of apoptosis and ADCP after binding to the CD20 antigen on the cell surface. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow. Rituximab is the first commercially available monoclonal antibody for the treatment of lymphoma and is currently approved for several NHL indications, including FL, chronic lymphocytic leukemia, and DLBCL. Rituximab is widely used in frontline and salvage regimens in B-cell NHL, either alone or in combination with chemotherapy. The estimated median terminal elimination half-life is 22 days (range 6.1 to 52 days), based on a population PK analysis of data from 298 NHL patients who received rituximab QW or once every 3 weeks (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).

4.4 Rationale for the Proposed Study

One approach to enhancing the efficacy of rituximab is the addition of other agents that could potentiate its activity. There is strong nonclinical evidence demonstrating that TAK-981 can synergize with rituximab to eliminate CD20+ NHL cells (Section 4.2.2).

TAK-981 has been shown to activate macrophages and NK cells. In the case of macrophages, TAK-981 induces human melatonin receptor (M1) polarization, upregulates Fc gamma receptors, and enhances phagocytosis and ADCP in an ex vivo assay. In the case of NK cells, TAK-981 promotes upregulation of the activation marker CD69 and the degranulation marker CD107, increases the number of IFNγ + NK cells in tumors, and enhances cytotoxicity and ADCC in an ex vivo assay. This mechanistic cooperation with ADCP and ADCC supports the combination of TAK-981 with IgG1 therapeutic monoclonal antibodies.

In vivo studies have demonstrated robust antitumor activity when TAK-981 is combined with rituximab in severe combined immunodeficient mice bearing human DLBCL xenograft models. Specifically, in the OCI-Ly-10 and TMD8 models the combination can reproducibly result in complete regression of all treated tumors at doses at which no CRs were achieved for either single-agent treatment. In the PHTX-166L PDX (patient derived xenograft) model, single agent TAK-981 and single agent rituximab showed only very modest tumor growth delay, but combination treatment resulted in longer-term growth delay and 1 complete regression out of 6 mice.

Although these tumor models lack lymphocytes, they retain an intact innate immune system, and the demonstrated activation by TAK-981 of macrophages and NK cells, key innate effector cells required for the antitumor activity of tumor-targeting antibodies such as rituximab, suggests that enhancement of ADCP and/or ADCC may provide a mechanistic rationale for the synergistic combination activity achieved in these models.

4.4.1 Rationale for the Starting Dose and Schedule

4.4.1.1 TAK-981

TAK-981 has been extensively characterized in preclinical studies (Sections 4.2.2 and 4.2.3) and is currently being evaluated as a single agent in the FIH study TAK-981-1002. The starting dose for the FIH study was based on minimum anticipated biological effect level with 3 mg of TAK-981

administered IV on Days 1, 4, 8, and 11 of a 21-day dosing cycle. As of 02 May 2019, 5 patients have received at least 1 dose of TAK-981 at the starting dose of 3 mg, administered as a single agent. No incidences of infusion-related reactions (IRRs) or CRS have been reported after a total of 22 doses (16 in Cycle 1 and 6 in Cycle 2).

After consideration of the emerging safety data from the ongoing FIH single-agent study (Study TAK-981-1002), with the agreement of the Study TAK-981-1501 investigators, the starting dose level for TAK-981 in combination with rituximab for this Phase 1 study is 10 mg administered on Days 1 and 8 of each 21-day dosing cycle. This dose level represents a 50% lower dose intensity than the 10 mg dose level in the FIH single-agent study. Alternative dosing schedules (eg, Day 1, or Days 1, 4, 8, and 11, or Days 1, 8, and 15 in 21-day cycles) may be investigated.

Rationale for the Phase 2 Dose of TAK-981 in This Combination Study:

Traditionally, the RP2D of cytotoxic anticancer agents was determined by DLT given the assumption that the highest tolerable dose could result in better therapeutic activity. For some current drugs, such as TAK-981, with new mechanisms of action (ie, drugs that target specific molecules involved in the proliferation and metastasis of cancer cells as the mechanism to kill or inhibit proliferation), the classical approach using only toxicity to define a RP2D may not be sufficient (Hansen et al. 2017). With targeted drugs, increasing doses beyond a certain level may not enhance the therapeutic activity, DLTs and a MTD may not be observed, and more serious TEAEs may only occur after multiple cycles of therapy (Shah et al. 2021). In addition to safety and tolerability, biological results such as PK, pharmacodynamics, and efficacy may also be useful in identifying a dose to evaluate in Phase 2 with these molecularly targeting agents, for which clinical benefit is not necessarily dose dependent. Therefore, the optimal method to define RP2D remains unclear in this setting (Shah et al. 2021) (Hansen et al. 2017).

As per protocol in study TAK-981-1501, the dose to be evaluated in the Phase 2 expansion could be the MTD based on observed DLTs following Bayesian logistic regression modeling (BLRM) guidance or a dose below MTD considering other non-DLT safety and tolerability information as well as other data, including but not limited to PK, pharmacodynamic, and exposure/response findings. Further, the TAK-981 + rituximab combination dose and schedule to be taken forward for future efficacy studies could be determined either at the end of Phase 1 or Phase 2, considering all these circumstances. Overall, the RP2D will be determined from the collective experience in the clinic, considering the safety data, preliminary PK data, preliminary pharmacodynamics data, and any observed early antitumor activity.

In Study TAK-981-1501, in addition to toxicity, other parameters such as PK, pharmacodynamics, and efficacy were considered in the decision regarding the dose(s) to be evaluated in the Phase 2 expansion. Dose-dependent pharmacological effects, defined by target engagement and Type 1 IFN signaling, have been reported with similar magnitude and duration of pharmacodynamic responses when administered alone or in combination with rituximab. These pharmacodynamic readouts were observed from the TAK-981 dose level of 60 mg and up to the dose level of 120 mg. Across the doses evaluated in this study, the PK of TAK-981 was linear with approximately dose-proportional increases in area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$). There was no accumulation of TAK-981 from C1D1 to C1D8 after either QW

or BIW dosing, and plasma exposures were similar when TAK-981 was administered alone or in combination with rituximab. PK/pharmacodynamics relationship modeling show dose-dependent target engagement that begins to plateau approximately at the 60 mg dose with a near maximal pharmacodynamic effect in terms of Type 1 IFN effector cell activation at the 120 mg dose of TAK-981. The currently available data in the dose- or exposure-response analyses have not been able to inform a dose selection, likely because of the small sample sizes in some of the dose cohorts in this Phase 1 dose escalation phase. As previously noted, in this study combining TAK-981 with rituximab, no DLTs were reported, an MTD was not identified, and dose modifications have been infrequent and similar across the QW dose cohorts. Moreover, antitumor activity has been seen across all QW dose levels evaluated.

Therefore, considering the totality of the data from this Study TAK-981-150, and factoring in safety, PK, and pharmacodynamics data from the FIH single-agent study (TAK-981-1002), upon implementation of Amendment 8, two TAK-981 doses (ie, 60 mg and 120 mg) will be evaluated in the Phase 2 expansion Cohorts B and C, in combination with rituximab.

TAK-981 will be evaluated at a dose of 120 mg QW (the upper dose tested in Phase 1) as well as at the dose of 60 mg QW (a lower yet biologically active dose) in a 21-day cycle, both in combination with a fixed dose of rituximab, in the Phase 2 expansion. The dose cohorts will be: Cohorts B 120 mg/C 120 mg and Cohorts B 60 mg/C 60 mg. This data will be used to generate supplementary efficacy, safety, and exposure/response data in both DLBCL (Cohort B, Figure 6.e) and FL (Cohort C, Figure 6.f) to inform dose selection for further development of TAK-981. Patients treated in Cohort A (Figure 6.d; another cohort of patients with DLBCL) will receive 120 mg QW of TAK-981 in combination with rituximab.

4.4.1.2 Rituximab

Rituximab will be administered at the clinically approved dose of 375 mg/m^2 IV. The rituximab dosing schedule was selected based on the recommended single-agent dosing regimen for this population with 4 QW administrations of rituximab, and evidence that a loading/maintenance dosing regimen enhances efficacy in pretreated NHL patients (Ghielmini et al. 2004; National Comprehensive Cancer Network 2019). This schedule is adapted to the TAK-981 schedule of Day 1 and 8 every 3 weeks with rituximab administered at 375 mg/m^2 in Cycle 1 on Days 1, 8, and 15, and on Day 1 of subsequent 21-day cycles until a discontinuation criterion is met.

4.4.2 Rationale for Tumor, Skin, and Blood Tissues Collection

4.4.2.1 Tumor Biopsies

Optional pre- and post-treatment tumor biopsies will be collected in Phase 1 to evaluate target engagement [redacted] Biomarker readouts may include determination of TAK-981–SUMO adduct formation and SUMO pathway inhibition in the tumor, as well as functional modulation of the immune response/cellular subsets in the tumor microenvironment.

[redacted]

[redacted]

Tumor biopsies, including archival tissues, are not applicable to patients enrolled in China.

4.4.2.2 Skin Biopsies

Skin punch biopsies will be collected to determine TAK-981-SUMO adduct formation and SUMO2/3 inhibition in a surrogate tissue. The collection of these biopsies may be discontinued once the sponsor has sufficient evidence of target engagement. No skin biopsies will be performed in Phase 2.

4.4.2.3 Blood

Blood samples will be collected to demonstrate TAK-981–SUMO adduct formation, SUMO pathway inhibition, and activation of an innate and/or adaptive immune response. [redacted]

4.5 Potential Risks and Benefits

TAK-981 is currently being evaluated in a single agent FIH study (TAK-981-1002), in addition to studies evaluating TAK-981 in the following combinations: TAK-981-1501, (this study with rituximab), TAK-981-1502 (with pembrolizumab), and TAK-981-1503 (with anti-CD38 monoclonal antibodies). The clinical benefits and risks have not yet been determined. Preliminary safety information is described in Section 4.2.5.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and SAEs by the sponsor.

In addition to safety, TAK-981 is currently being evaluated for preliminary efficacy across the 4 ongoing studies (noted above). As of the IB data cutoff, clinical efficacy data is still emerging. In this study, initial efficacy is being reported, but further follow-up and assessments are needed.

4.5.1 Potential Effects of TAK-981 Based on TAK-981 Nonclinical and Clinical Studies

The potential AEs/risks of TAK-981 are based on findings from the nonclinical studies with the emerging safety data from ongoing clinical studies: hematologic effects (lymphocytopenia with/without associated opportunistic infection; anemia, thrombocytopenia, neutropenia); injection site reactions; IRRs and potential for CRS; and changes in renal function (Refer to Section 8.10). Safety data (as of 28 June 2021) obtained from the dose escalation cohorts across all ongoing studies demonstrated that the most common TEAEs (>20%) are fatigue, pyrexia, nausea,

diarrhea, chills, and headache; TEAEs consistent with induction of IFN signaling. The only serious adverse reaction considered expected for safety reporting purposes across the ongoing TAK-981 studies is pyrexia. The single agent MTD (in Study TAK-981-1002) has been identified as 120 mg with evaluation continuing in the ongoing studies of TAK-981 in combination with pembrolizumab or a monoclonal antibody (studies TAK-981-1502 and TAK-981-1503, respectively) as well as from this study (TAK-981-1501). For additional details, refer to Section 4.2.5 and the TAK-981 IB.

Further details for TAK-981 administration and safety events management can be found in Section 8.1, Section 8.10, and the Guidance for Investigator section of the IB.

Lymphoid and Hematopoietic Effects

Dose-dependent reversible or partially reversible lymphoid/hematopoietic effects, including peripheral lymphopenia and decreased cellularity in lymph nodes, spleen, thymus, and gut-associated lymphoid tissue were observed in repeat-dose toxicity studies in rats and dogs. Decreased cellularity of lymphoid tissues contributed to decreases in white blood cell counts. These findings could be associated with increased susceptibility to certain forms of infection that were not observed in the GLP toxicology studies.

In this study, absolute lymphocyte counts and subpopulations will be monitored. Prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes virus is recommended for prolonged CD4 counts below 200/µL.

As of the IB data cutoff for this report and the ongoing clinical studies, transient decrease lymphocyte count related to TAK-981 has been reported (3.7%). Opportunistic infections have not been reported to date; however, herpes virus reactions have been observed (1.5% related to TAK-981). These reactions are self-limited and resolve within 14 days. (Refer to the IB for current details.)

Effects in Renal Pelvis

In dogs, at the higher doses following repeat daily or BIW dosing, there was reversible to partially reversible inflammation and arteriolar fibrinoid necrosis localized at the renal pelvis; this did not involve either renal cortex or medulla. The lesions had no repercussion on kidney function or conventional urinary test parameters.

Inflammation in the renal pelvis suggests a local effect of concentrated drug or a metabolite. No clinically significant safety concerns have been reported as of the IB data cutoff date of 28 June 2021. Patients will be asked to maintain adequate hydration (1.5-2 L/day) 48 hours before initiating therapy; IV fluid administration on C1D1 will be recommended for those who cannot maintain adequate oral hydration. Patients will be monitored for renal function, and in patients with significant alterations in urinalysis, urine sediment analysis will be required.

IRRs and Potential for CRS

The mechanism of action of TAK-981 involves type 1 IFN signaling; as a result, there is potential for infusion reactions and CRS. Serum cytokine levels were examined in the BIW GLP toxicity studies in rats and dogs. Modest increases in MCP-1, IFN gamma-induced protein 10 (rats only),

and RANTES (rats only) were observed. There were no increases in cytokines related to CRS, including interleukins (ILs), IL-2, IL-6, and IL-10; IFNγ; granulocyte-macrophage colony-stimulating factor; and tumor necrosis factor-alpha, observed.

An in vitro CRA was performed with human whole blood for hazard identification of clinically significant CRS. There were no effects on cytokines typically associated with CRS; TAK-981 – related effects were limited to moderate increases in IP-10 at ≥0.5 µM (for details see Section 4.2.4).

In a single dose safety pharmacology study, acute and transient mildly increased body temperature and reactive increased heart rate without changes in blood pressure were observed in dogs from 6 to 24 hours after the infusion. In a single dose non–GLP-compliant dog toxicity study, fever was considered a DLT at the high dose of 12 mg/kg. Non–dose-limiting increases in body temperatures were noted in studies with daily and QW dosing at ≥3 mg/kg. No changes in body temperature, heart rate, or respiratory rate were observed in the GLP-compliant BIW dog study. [redacted]

As a precaution for IRRs/CRS, the first 3 patients enrolled at given dose level in the Phase 1 portion of the study will be hospitalized for a minimum of 18 hours after the first infusion of TAK-981. For the remaining infusions (and only in cases where no IRRs are being observed), the patient will be observed a minimum of 2 hours after end of infusion of the last study drug, and can only be discharged if clinically stable (for details about drug administration and monitoring, see Section 8.1).

As an additional precautionary measure, during dose escalation only, patient enrollment is staggered between the first and second patients at all dose levels by 72 hours. At each dose level, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through Cycle 1 Day 4 without clinically significant acute toxicities (Section 6.2).

As per the IB, across the ongoing clinical studies, infusion related TEAEs (eg, fever [29.6%], chills [21.5%], fatigue [23.0%]) have been consistent with transient flu-like symptoms associated with the induction of type I IFN signaling; however, other than the transient type I IFN medicated TEAEs, no other TAK-981–related immune-related AEs have been observed. Upregulation of the type I IFN gene signature in peripheral blood was first detected in clinical studies at 60 mg of TAK-981, providing transcriptional evidence of a type I IFN response. Across the ongoing clinical studies, CRS has been reported in 10 (7.4%) patients. The highest CRS grade reported was Grade 1 in 5 (3.7%) patients and was Grade 2 in 5 (3.7%) patients; some patients experienced >1 CRS event. In all cases, oral antipyretics, in addition to either low flow oxygen for patients with hypoxia or IV fluids with no vasoactive drug support for patients with low blood pressure, were sufficient to manage the CRS. No patient with CRS has required anti–IL-6 directed therapies. (Refer to the IB for further details.)

Injection Site Reactions

Partially reversible effects at the injection site, including potentiation of procedure-related subcutaneous perivascular hemorrhage, inflammation, and necrosis, were observed in rats only. The shorter needle length and frequent movement of conscious rats likely resulted in extravasation, and chemical irritation due to the acid pH (3.5) of the dosing solution could have been a contributing factor. Injection site reactions related to TAK-981 have been infrequently reported (1.5%; all Grade 1) in the ongoing clinical studies.

Sites will be informed to enforce careful observation of the infusion site in case a peripheral vein is used for administration. In general, infusion through a central line or subcutaneous reservoir is preferred for TAK-981 administration (see Section 8.1). (Refer to the IB for further details)

Reproductive and Development Toxicity

Reproductive and developmental toxicity studies have not yet been conducted; therefore, the effects of TAK-981 on fertility and the developing fetus are currently unknown. Reproductive tissues were weighed and examined microscopically as part of the GLP-compliant repeat-dose toxicity studies with QW or BIW dosing in sexually mature rats and dogs of both sexes. TAK-981–related reproductive findings were not observed in either rats or dogs with BIW dosing, or in dogs with QW dosing. However, in the rat study with QW dosing, at ≥20 mg/kg there was reversible single-cell necrosis in multiple male and female reproductive tissues and inflammation in the prostate gland. In addition, there was partially reversible acinar cell atrophy in the male mammary gland at ≥5 mg/kg. Additionally, in a non−GLP-compliant, 7-day repeat-dose toxicity study in male rats, TAK-981−related effects were noted in multiple reproductive tissues in animals that also had significant systemic toxicity, including minimal to mild single-cell necrosis of the epithelium (≥10 mg/kg), and, at 40 mg/kg, minimal to mild atrophy, karyomegaly, increased mitotic figures, and/or degeneration/necrosis.

Female partners of male patients participating and female patients participating in this study should avoid becoming pregnant.

Genotoxicity

TAK-981 was not mutagenic in an in vitro bacterial mutagenesis Ames assay. In an in vivo rat bone marrow micronucleus assay, TAK-981 increased induction of micronuclei and was considered to be positive for in vivo genotoxicity at ≥5 mg/kg. TAK-981 was considered clastogenic in an in vitro chromosomal aberration test using human peripheral blood lymphocytes. In compliance with ICH S9 guidance [ich.org/products/guidelines/safety/article/safety-guidelines.html]), a carcinogenicity assessment is not planned.

The potential effects listed above are based on toxicology findings in the nonclinical studies and the emerging safety data from ongoing clinical studies with TAK-981. The nonclinical data may or may not present with similar severity in humans. It is possible that administration of TAK-981 will result in toxicities that were not observed or predicted from the completed nonclinical studies conducted in animals or previously observed in ongoing clinical studies. To mitigate the inherent

risks in clinical studies of TAK-981, patients will be carefully monitored closely for signs and symptoms of adverse reactions with appropriate management of these events.

4.5.2 Potential Effects of Rituximab

Rituximab toxicities are generally associated with B cell depletion, infusion reactions, and/or tumor lysis syndrome (TLS). For detailed information regarding the safety of rituximab administration please refer to the United States Food and Drug Administration (FDA)-approved package insert (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).

4.5.3 TAK-981 in Combination with Rituximab

Nonclinical toxicology studies with the combination of TAK-981 and rituximab, or other anti-CD-20 agents, were not conducted and are not warranted per ICH S9 (ich.org/products/guidelines/safety/article/safety-guidelines.html). Compared to TAK-981 alone, synergistic toxicity, as assessed by increased mortality or significant decreases in body weight, was not observed in mouse tumor-bearing models administered TAK-981 in combination with rituximab. Based on the safety profile of TAK-981 (nonclinical) and rituximab (clinical) described above, there is potential for some toxicity overlap between the IRR of rituximab and the potential for IFN signaling induced IRR/ CRS of TAK-981. However, based on the non-clinical CRA, the CRS risk of TAK-981 can be considered low. In this study, on C1D1, rituximab will be administered per standard of care administration guidance before TAK-981 and with a separation of 1 hour. Another potential overlap for the 2 drugs is the effects on the immune system, specifically on the B-cell arm of adaptive immunity. It is well-known that rituximab can produce profound and prolonged B cell depletion with no major effect on T cells. Lymphocyte subpopulations will be monitored frequently during the study to assess the potential impact on the cellular immunity.

Finally, due to the risk for TLS associated with rituximab monotherapy and the expected enhancement of treatment efficacy with the proposed combination, TLS risk stratification, monitoring, and precautions will be observed.

As of 28 Jun 2021, the most common TEAE was pyrexia in this study (TAK-981-1501). Other common TEAEs were diarrhea, chills, dizziness, fatigue, and nausea. There were no reports of CRS or DLTs as of this data cutoff. Refer to current IB for more details.

Altogether, the potential overlap of risks for the combination are considered to be low and will be monitored throughout the study.

4.5.4 Coronavirus Disease 2019 Pandemic

The coronavirus disease 2019 (COVID-19) pandemic has affected health care and specifically cancer care broadly across the globe. Based on current knowledge, the benefit/risk assessment for patient participation in this study remains favorable. The benefit/risk considerations for patient participation should be evaluated by the investigator on a patient-by-patient basis taking into consideration the current local situation, guidelines, and recommendations. Investigators should

follow local recommendations and guidelines with regards to COVID-19 precautions, vaccination, and treatment, see Section 8.6.3.3 and 8.8.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

Phase 1:

- To determine the safety and tolerability of TAK-981 in combination with rituximab in patients with r/r NHL.
- To establish the RP2D of TAK-981 in combination with rituximab.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL indications.

5.1.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK profile of TAK-981 in combination with rituximab.

Phase 1:

- To determine the MTD and/or PAD of TAK-981 when administered in combination with rituximab.
- To assess the preliminary antitumor activity of TAK-981-rituximab combination.
- To assess target engagement of TAK-981 (SUMO-TAK-981 adduct formation) and SUMOylation pathway inhibition in blood and skin.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with rituximab in select r/r NHL as measured by disease control rate (DCR), duration of response (DOR), TTP, and progression-free survival (PFS).
- To evaluate the safety and tolerability of TAK-981 in combination with rituximab.

5.1.3 Additional/Exploratory Objectives

5.1.3.1 Exploratory Objectives (Global Study; Not Applicable to Patients Enrolled in China)

[redacted]

5.1.3.2 Exploratory Objectives (China-Specific)

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

Phase 1:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0; except CRS which will be graded according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS.

- Occurrence of DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- ORR (CR + PR) as defined by the investigator according to Lugano Classification for lymphomas.

5.2.2 Secondary Endpoints

The secondary endpoints for this study are:

- PK parameters after the first dose of TAK-981 on C1D1 and Cycle 1, Day 8 (C1D8) (data permitting):
  - C_{max}.
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the plasma concentration-time curve from time 0 to time t (AUC_{0-t}).
  - $AUC_{0-\infty}$.
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Total clearance (CL) after IV administration.
  - V_{ss}.

Phase 1:

- ORR, DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in skin/blood.

Phase 2:

- Frequency, severity, and duration of TEAEs and laboratory abnormalities for all dose groups according to the NCI CTCAE, Version 5.0; except CRS, which will be graded according to ASTCT Consensus Grading for CRS.
- DCR, DOR, TTP, and PFS as assessed by the investigator according to Lugano Classification for lymphomas.

5.2.3 Additional/Exploratory Endpoints

5.2.3.1 Exploratory Endpoints (Global Study; Not Applicable to Patients Enrolled in China)

[redacted]

[redacted]

Collection of samples for exploratory endpoints are dependent upon local guidelines and regulations (including feasibility of sample export), as well as institutional review board (IRB)/independent ethics committee (IEC) approval.

5.2.3.2 Exploratory Endpoints (China-Specific)

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This study is an open-label, multicenter, Phase 1/2 study investigating the combination of TAK-981 and rituximab in adult patients with r/r CD20+ NHL. The study will be conducted in 2 parts:

1. Phase 1 dose escalation guided by BLRM in patients with both indolent and aggressive r/r CD20+ NHL.
2. Phase 2 study with 3 treatment arms with select r/r FL and r/r DLBCL indications, conducted according to an adaptive 2-stage design for a single proportion.

The study will consist of a screening period (Day -28 to -1), a treatment period, and an end-of-treatment (EOT) visit 30 (+10) days after the last dose occurs (or when treatment is discontinued for any reason). A PFS follow-up period lasting until disease progression or the patient's next line of therapy or a maximum of 12 months for each patient will be performed to monitor disease progression status. After the occurrence of progressive disease (PD), or start of alternative therapy, patients will continue to have OS follow-up visits that may be performed by phone contact, email, mail, or retrieval from online or other databases. The OS information will be collected every 12 weeks (±1 week) after the last dose of study drug until death or the conclusion of the study, whichever occurs first (refer to Section 9.9 for more details). Day 1 of the study (baseline) will be defined as the first day a patient receives TAK-981. One cycle of treatment will be defined as 21 days. Patients will be asked to attend clinic visits at regular intervals during the study for safety and efficacy assessments.

Patients will receive treatment with TAK-981 and rituximab for up to 12 months or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the

study or study drugs occurs. Treatment may be continued beyond disease progression, with sponsor approval, if, in the opinion of the investigator, the patient continues to experience clinical benefit.

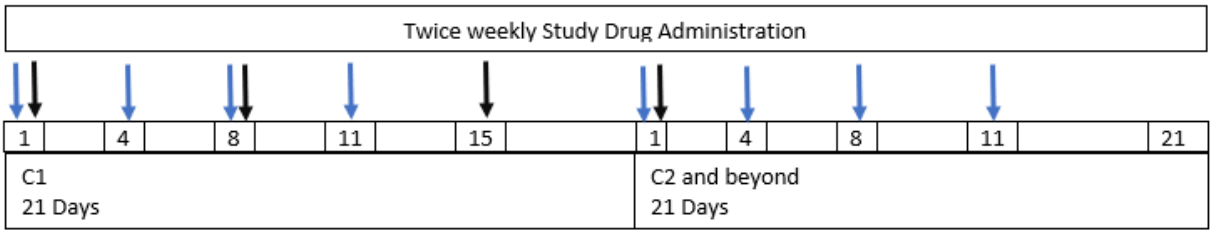
6.2 Phase 1 Study Design

The dose-finding, dose-escalation part of the study will enroll patients with aNHL (mantle cell lymphoma patients are also allowed) and iNHL. Patients will be treated in cohorts with increasing doses of TAK-981 administered IV as a 1-hour infusion on Days 1 and 8 followed by a fixed dose of rituximab of 375 mg/m^2 administered IV on Days 1, 8, and 15 during Cycle 1 and on Day 1 of each subsequent cycle (from Cycle 2 Day 1 onwards). Cycle duration is 21 days. (Study drug administration details in Section 8.1.) Evaluation of alternative TAK-981 dosing schedules (eg, Days 1, 4, 8, and 11 in 21-day cycles) may be permissible after discussions between the sponsor and the investigators, based on data emerging across the program.

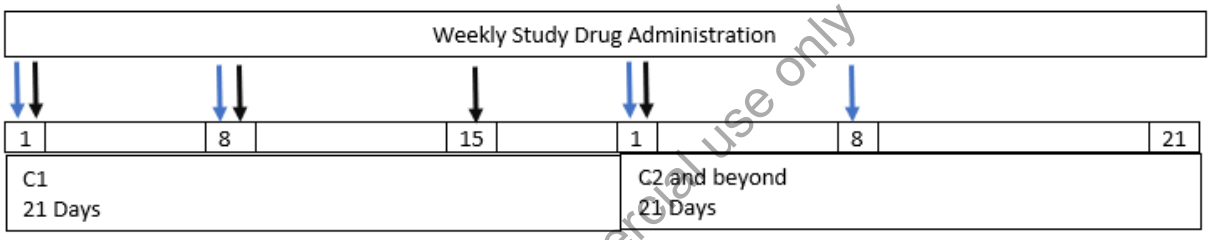
Dose-escalation intervals progress from 10 mg to 160 mg. The starting dose for TAK-981 is justified in Section 4.4.1. As of Amendment 6, Phase 1 patients are being enrolled to the 90 mg of TAK-981 BIW and 120 mg of TAK-981 QW (2 weeks on and 1 week off) cohorts in a 21-day cycle.

TAK-981 in combination with rituximab will be administered until a discontinuation criterion is met (Section 8.6.4).

Figure 6.a TAK-981-1501: Schedules for TAK-981 Twice or Once Weekly and Rituximab Dosing



Blue arrow: TAK-981; Black arrow: Rituximab



Blue arrow: TAK-981; Black arrow: Rituximab

Note: Evaluation of alternative TAK-981 dosing schedules (ie, twice weekly on Days 1, 4, 8, and 11; or once weekly on Days 1 and 8 in 21-day cycles) may be permissible only after discussions between the sponsor and the investigators.

Dose escalation will be cohort-based with an adaptive design using a BLRM model with Escalation with Overdose Control (see Appendix H for details). Approximately 35 patients will be enrolled until either MTD or a PAD is identified. A minimum of 3 patients will be enrolled in the dose level 1 cohort. Dose escalation and cohort expansion decisions are reviewed and approved by the Safety Monitoring Committee (SMC) consisting of sponsor representatives and investigators.

For the first infusion (C1D1) of TAK-981 every patient needs to be hospitalized for drug administration and observation for a minimum of 18 hours after the end of infusion of TAK-981. Hospitalization is not required if expansion after 3 patients in a dose level or expansion of previously cleared dose level and only if infusion reaction risk is considered low based on previous experience. If grade 3 or greater IRR or CRS are not observed at PAD or MTD, or if the safety data from the ongoing FIH TAK-981-1002 study support the removal of the requirement of hospitalization for the first dose of TAK-981, the decision will rely on the SMC.

Patient enrollment will be staggered between the first and second patients by 72 hours during dose escalation at all dose levels. At each dose level, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through Day 4 (72 hours) without clinically significant acute toxicities. If more than 3 patients are to be enrolled in a dose level or if

de-escalation is indicated, staggering will not be required unless indicated by safety findings. Dose-escalation decisions will be made by the SMC as defined in Section 8.5.

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). A DLT will be defined as any of the events described in detail in Section 8.2 occurring during Cycle 1 unless they are considered by the investigator to be clearly unrelated to therapy with TAK-981 in combination with rituximab. TEAEs meeting DLT definitions occurring in later cycles will determine the suitability of the PAD/MTD as the RP2D.

Intrapatient dose escalation will be permitted only when patients in the next dose level cohort have completed assessment for Cycle 1 and a decision has been made that this dose level does not exceed the MTD.

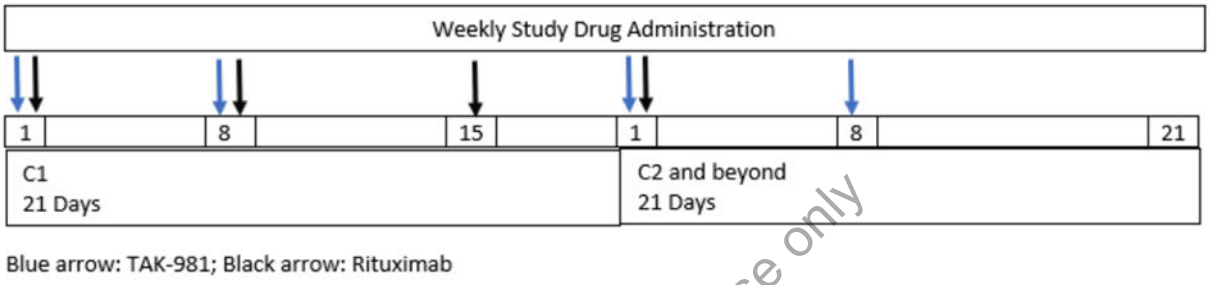
The SMC will select the dose to be used for the Phase 2 part of the study. It can be primarily the MTD based on the observation of DLTs, and following BLRM guidance as detailed in Section 8.5. A dose below the MTD can be selected for Phase 2 if it is recommended by other non-DLT safety and tolerability information. PK and pharmacodynamic information may also recommend using a dose below the MTD. The TAK-981/rituximab combination MTD, PAD, and schedule to be taken forward for our future efficacy studies will be determined either at the end of Phase 1 or Phase 2 considering all these circumstances.

6.3 Phase 2 Study Design

The Phase 2 part of the study uses a non-randomized, open-label, uncontrolled, parallel arm design that will enroll 1 cohort of patients with FL and another 2 cohorts of patients with DLBCL, one with patients that have relapsed after a chimeric antigen receptor T-cell therapy (CAR-T) that has been approved by a health authority, and another one for patients that have progressed after 2 or 3 lines of systemic therapy and have not received prior therapy with commercially available CAR T-cells. The primary objective during Phase 2 is to assess the efficacy of TAK-981 in combination with rituximab as measured by ORR per Lugano criteria using an adaptive 2 stage design for a single proportion. For Stage 1, each cohort will be analyzed when a prespecified number of patients (as defined in Section 13.3) have been enrolled and had the potential to have a least 1 post-treatment radiologic evaluation of the disease. If the prespecified minimal response rate is not achieved in the first stage for a given cohort, that cohort will be closed to enrollment. However, if a clear clinical benefit has been observed for patients in the cohort (eg, a majority of patients have recorded stable disease at Week 8 and no CR or PR is recorded) then enrollment into Stage 2 may be allowed for this cohort. If the required response rate during Stage 1 or a good clinical benefit is observed for a particular cohort as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients for that cohort has been reached (as defined in Section 13.3). The final analysis of the primary endpoints for each cohort will be performed when all ongoing patients have completed the 6-month disease assessment/survival follow-up.

TAK-981 will be evaluated at a dose of 120 mg QW (the upper dose tested in Phase 1) as well as at the dose of 60 mg QW (a lower yet biologically active dose) in a 21-day cycle, both in combination with a fixed dose of rituximab, in the Phase 2 expansion. The dose cohorts will be: Cohorts B 120 mg/C 120 mg and Cohorts B 60 mg/C 60 mg. This data will be used to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

Figure 6.b TAK-981-1501: Schedule for TAK-981 Once Weekly and Rituximab Dosing



Note: Evaluation of TAK-981 dosing schedule, ie, once weekly on Days 1 and 8 in 21-day cycles.

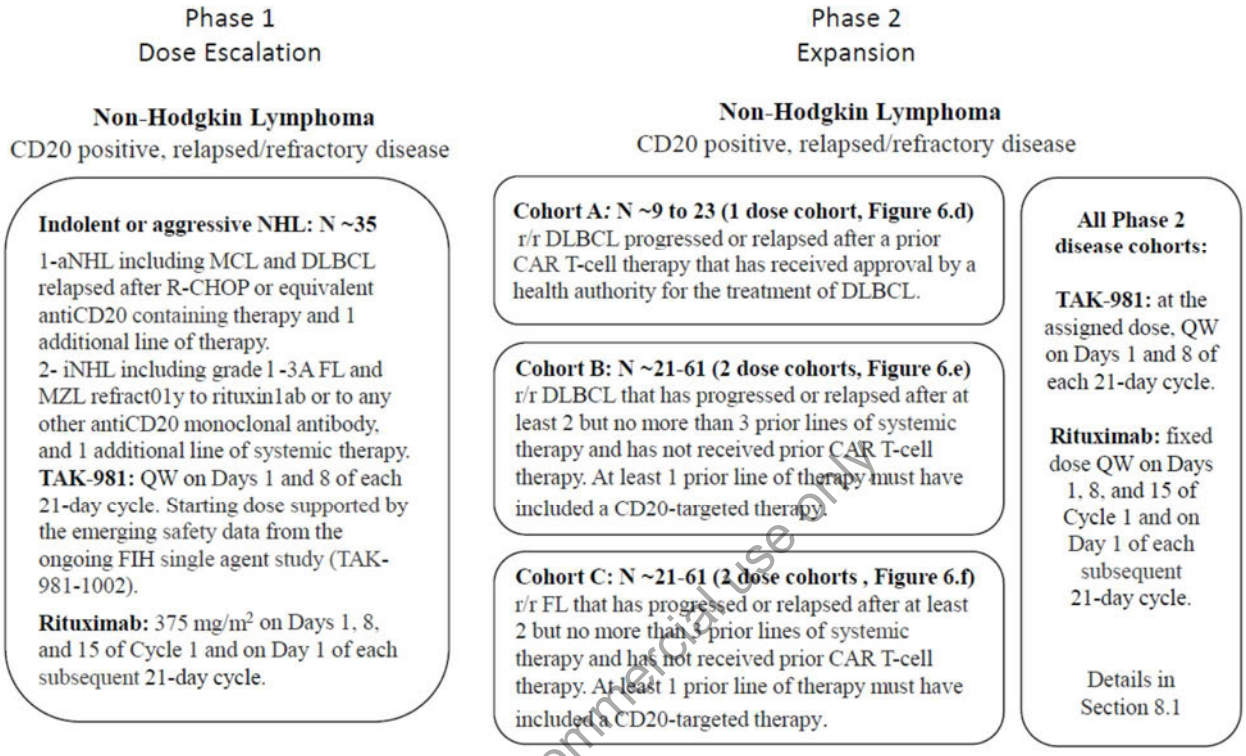
During the Phase 2 portion, patients will be concurrently enrolled and the sponsor/designee will assign patients to a respective cohort and, for Cohorts B and C only, to a respective TAK-981 dose group (B 120 mg, B 60 mg, C 120 mg, or C 60 mg). All patients in Cohort A will receive the same 120 mg dose. Hospitalization for C1D1 TAK-981 administration is not required.

During Phase 2, an Independent Data Monitoring Committee (IDMC) will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study.

Patients enrolled in sites in China will participate in Phase 2 of the study.

The overall study schematic is displayed in Figure 6.c.

Figure 6.c TAK-981-1501 Study Schematic of Phase 1 and Phase 2



aNHL: aggressive Non-Hodgkin Lymphoma; CAR: chimeric antigen receptor; DLBCL: diffuse large B-cell lymphoma; FIH: first-in-human; FL: follicular lymphoma; iNHL: indolent Non-Hodgkin Lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; QW: once weekly; R-CHOP: rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin) and prednisone; r/r: relapse/refractory.

For more details on Cohorts A, B, and C, please refer to Figure 6.d, Figure 6.e, and Figure 6.f, respectively.

Figure 6.d [redacted]

Figure 6.e [redacted]

Figure 6.f [redacted]

6.4 Number of Patients and Sites

A total of approximately 180 patients will be enrolled in the study. Approximately 35 patients will be enrolled in the Phase 1 at approximately 12 study centers. During Phase 2, up to 23 or 61 patients (Figure 6.c) will be enrolled in the CAR T-cell–relapsed DLBCL of Cohort A or the r/r DLBCL Cohort B and the r/r FL Cohort C, respectively, the latter 2 cohorts treated with no prior commercially available CAR-T. Up to a total of approximately 70 sites in United States, Canada, European Union, Asia, and/or globally will be required for this study.

In addition, approximately 25 patients each, without prior treatment with commercially available CAR-T, will be added to Cohorts B (r/r DLBCL) and C (r/r FL), and treated with TAK-981 60 mg QW and rituximab, to generate supplementary efficacy, safety, and exposure/response data to inform dose selection for further development of TAK-981.

6.5 Duration of Study

6.5.1 Duration of an Individual Patient's Study Participation

Patient participation will include screening, treatment, and follow-up. Screening will last up to 28 days before the first dose of study drug, during which the patient's eligibility and baseline characteristics will be determined. Treatment with TAK-981 with rituximab will be administered for up to 12 months or until patients meet any of the discontinuation criteria in Section 8.6.4. Patients with demonstrated clinical benefit may continue treatment beyond 12 months with the agreement of the sponsor. These patients can continue receiving treatment in this study or any of the poststudy access modalities described in Section 6.5.5. Patients who discontinue rituximab for reasons described in Appendix I (Rituxan (rituximab) Injection for Intravenous Use 2019) may continue TAK-981 treatment; however, patients cannot remain on rituximab as a single agent once TAK-981 has been discontinued. In that case, patients will undergo the EOT visit.

Patients should attend the EOT visit 30 days (+10 days) after receiving their last dose of TAK-981 or before the start of subsequent systemic anticancer therapy, whichever occurs first, to permit detection of any delayed TEAEs and resolution of ongoing events. Patients with unresolved TEAEs will continue the periodic safety follow-up until complete resolution or stabilization (established as sequelae) occurs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 12 weeks ±1 week from last dose of study drug until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, or study termination (Section 9.6), whichever occurs first. During Phase 2, patients who stop treatment due to PD will be followed every 12 weeks (±1 week) after documented PD for OS until death, loss to follow-up, consent withdrawal, or study termination for up to 12 months following the last day the patient discontinues or completes treatment, or until 50% of patients have died, whichever occurs first. (Additional detail in Section 9.9)

6.5.2 End of Study/Study Completion Definition and Planned Reporting

The final data cutoff for the clinical study report will be conducted after all patients have been discontinued from treatment or transferred to a long-term safety study, a single-patient investigational new drug application, or a similar program (Section 6.5.5). The estimated time frame for study completion is approximately 72 months.

6.5.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary (Phase 1):		
Frequency, severity, and duration of TEAEs overall and per dose level	Standard safety assessments	Up to 72 months
Number of patients with DLTs per dose level	Standard safety assessments	Up to 72 months
Number/percentage of patients with clinically significant laboratory values	Standard safety assessments	Up to 72 months
Primary (Phase 2):		
ORR as defined by the investigator according to Lugano classification for lymphomas	Standard efficacy assessments	Up to 72 months
Secondary:		
Data permitting, PK parameters after the dose administration of TAK-981 on C1D1 and C1D8: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2z}$, CL, V_{ss}	Standard PK parameters to allow determination of PK profile	Up to 72 months
DCR	DCR	Up to 72 months
DOR	DOR	Up to 72 months
PFS	PFS	Up to 72 months
TTP	TTP	Up to 72 months
TAK-981–SUMO adduct formation; SUMO pathway inhibition	TAK-981–SUMO adduct formation; SUMO pathway inhibition in either skin tissue or in blood (Phase 1 only).	Up to 72 months

AUC_{0-t}: area under the plasma concentration-time curve from time 0 to time t; $AUC_{0-\infty}$: area under the plasma concentration-time curve from time 0 to infinity; C1D1: Cycle 1, Day 1; C1D8: Cycle 1, Day 8; CL: total clearance after intravenous administration; C_{max}: maximum observed plasma concentration; DCR: disease control rate; DLT: dose-limiting toxicity; DOR: duration of response; ORR: overall response rate; PFS: progression-free survival; PK: pharmacokinetic; SUMO: small ubiquitin-like modifier; TEAE: treatment-emergent adverse event; $t_{1/2z}$: terminal disposition phase half-life; TTP: time to progression; t_{max}: time of first occurrence of C_{max}; V_{ss}: volume of distribution at steady state after intravenous administration.

6.5.4 Total Study Duration

It is anticipated that this study will last for approximately 72 months.

6.5.5 Poststudy Access

Subjects who have met the primary (and secondary) endpoints of the study and, in the opinion of the investigator and confirmed by the sponsor, experienced a clinically important benefit from TAK-981 in combination with rituximab may continue to receive TAK-981 or the combination in an extension phase of this study or will be given the opportunity to enroll in a separate open-label rollover study or have the possibility of using an individual patient investigational new drug to continue receiving both study drugs, where permitted by local regulations.

Additionally, these patients should have no alternative therapeutic option and would be harmed without continued access.

Duration of Poststudy Access

Continued access to TAK-981 or the combination with rituximab for subjects will be terminated for those individuals who no longer benefit from TAK-981 or the combination (eg, they have completed the recommended course of therapy or their disease has resolved), the benefit-risk no longer favors the individual, if TAK-981 ± rituximab becomes available either commercially or via some other access mechanism, or when an alternative appropriate therapy becomes available. Poststudy access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of TAK-981 has been suspended or stopped by the sponsor, or the TAK-981 can no longer be supplied.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Adults ≥18 years old.
2. Patient populations:
   a) For Phase 1 Dose Escalation:
      - aNHL including mantle cell lymphoma and DLBCL histologies such as transformed DLBCL from low-grade lymphoma (follicular or others), DLBCL associated with small-cell infiltration in bone marrow, B-cell lymphoma with intermediate features between DLBCL and Burkitt's lymphoma or with intermediate features between DLBCL and Hodgkin lymphoma, FL grade 3B, and aggressive B-cell lymphoma unclassifiable who must have previously received rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine, (Oncovin) and prednisone (R-CHOP) (or equivalent anti-CD20 containing therapy) and 1 additional line of therapy in the r/r setting.
      - iNHL (including FL of grades 1–3A and marginal zone lymphoma) refractory to rituximab or to any other anti-CD20 monoclonal antibodies, who have received at least 1 prior systemic therapy for r/r iNHL:
        – Rituximab or anti-CD20 refractoriness is defined as failure to respond to, or progression during, any previous rituximab/anti-CD20-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab or anti-CD20 dose.

          Note: The minimum qualifying rituximab/anti-CD20 dose is 1 full cycle (ie, weekly x 4 doses monotherapy or 1 complete dose if combined with chemotherapy). Prior anti-CD20 antibody or cytotoxic drugs may have been administered as single agents or as components of combination therapies. Each

repeated course of the same single agent or combination is considered an independent regimen.

b) For Phase 2, the following confirmed CD20 positive:

- r/r DLBCL progressed or relapsed after a prior CAR T-cells therapy that has received approval by a health authority for the treatment of DLBCL (Cohort A).
- r/r DLBCL that has progressed or relapsed after at least 2, but no more than 3 prior lines of systemic therapy and has not received prior cellular therapy. At least one prior line of therapy must have included a CD20-targeted therapy (Cohort B).
- r/r FL that has progressed or relapsed after at least 2, but no more than 3 prior lines of systemic therapy. At least 1 prior line of therapy must have included a CD20-targeted therapy (Cohort C).

3. Patients must be considered ineligible for, in the opinion of the investigator, or must have refused ASCT.
4. Eastern Cooperative Oncology Group (ECOG) performance score of ≤2.
5. Adequate bone marrow function per local laboratory reference range at screening as follows:
   - Platelet count ≥75.0 × 10^9/L, Grade 2 thrombocytopenia (platelet count ≥50.0 × 10^9/L) is allowed if it is clearly due to marrow involvement with no evidence of myelodysplastic syndrome or hypoplastic bone marrow if found. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L. Hemoglobin ≥85 g/L (RBC transfusion allowed ≥14 days before assessment).
6. Adequate renal and hepatic function, per local laboratory reference range at screening as follows:
   - Calculated creatinine clearance ≥30 mL/min calculated with Cockcroft-Gault formula.
   - Potassium levels ≥ lower limit of normal. For potassium > upper limit of normal (ULN) discussion with Takeda medical monitor/designee recommended.
   - Aspartate aminotransferase and alanine aminotransferase ≤3.0× the ULN of the institution's normal range; bilirubin ≤1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 × ULN, per discussion between the investigator and the medical monitor.
7. Left ventricular ejection fraction (LVEF) ≥40%; as measured by echocardiogram or multiple gated acquisition (MUGA) scan.
8. Suitable venous access for safe drug administration and the study-required PK and pharmacodynamic sampling.
9. Have at least 1 bidimensionally measurable lesion per Lugano Classification (eg, measurable node >1.5 cm in its largest dimension; measureable extranodal lesion >1.0 cm in longest

diameter) by computed tomography (CT). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

10. Willing to consent to 1 mandatory pretreatment and 1 on-treatment skin biopsy during Phase 1. The skin biopsy entry requirement may be discontinued by the sponsor once there is enough pharmacodynamic evidence of target engagement.
11. For patients enrolled in Phase 2, if available, mandatory submission of archival tumor tissue acquired ≤12 months prior to screening. Tumor tissue, including archival tissue, is not applicable to patients enrolled in China.
12. Recovered to Grade 1, baseline or established as sequela, from all toxic effects of previous therapy (except alopecia, neuropathy, autoimmune endocrinopathies with stable endocrine replacement therapy, neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [any of Grade 1, 2, permitted if directly related to bone marrow involvement]).
13. Women of childbearing potential 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 through 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 and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 12 months after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).
14. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 12 months after the last dose of study drug, or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
15. Subject has provided informed consent.

16. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

7.2 Exclusion Criteria

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

1. CNS lymphoma; active brain or leptomeningeal metastases, as indicated by positive cytology from lumbar puncture or CT scan/magnetic resonance imaging (MRI).
2. Hypersensitivity to TAK-981, rituximab, or any component of the drug product.
3. History of Grade ≥3 IRR that lead to permanent discontinuation of previous rituximab treatment.
4. Previous participation in the TAK-981-1002 clinical study.
5. Posttransplantation lymphoproliferative disease except relapsed NHL after ASCT.
6. Undergone ASCT or treatment with cellular therapy including CAR T within ≤12 weeks of TAK-981 dosing.
7. Prior allogeneic hematopoietic stem-cell transplantation.
8. Lymphomas with leukemic expression.
9. Prior anticancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 5 half-lives before TAK-981 dosing, whichever is shorter. Low dose steroids (oral prednisone or equivalent ≤20 mg per day), hormonal therapy for prostate cancer or breast cancer (in adjuvant situation), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed.
10. Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.
11. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor that would substantially increase the risk-benefit ratio of participating in the study. This includes but is not limited to acute myocardial infarction or unstable angina within the last 6 months; uncontrolled diabetes mellitus; significant active bacterial, viral, or fungal infections; severely immunocompromised state; severe non-compensated hypertension and congestive heart failure New York Heart Association Class III or IV; ongoing symptomatic cardiac arrhythmias of >Grade 2, pulmonary embolism, or symptomatic cerebrovascular events; or any other serious cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy). Chronic atrial fibrillation on stable anticoagulant therapy is allowed.
12. Known chronic hepatitis C and/or positive serology (unless due to vaccination or passive immunization due to Ig therapy) for chronic hepatitis B. Known HIV infection.
13. Second malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected

colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy as defined in Exclusion Criterion 9.

14. Receipt of any live vaccine within 4 weeks of initiation of study treatment.
15. Active, uncontrolled autoimmune disease requiring >20 mg of prednisone or equivalent, cytotoxics, or biologicals.
16. Corticosteroid use within 1 week before the first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. Patients requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for lymphoma control or white blood cell count lowering are not eligible.
17. History of medical or psychiatric illness likely to interfere with the ability to comply with protocol requirements or give informed consent.
18. Patients with baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, >470 ms for women and >450 ms for men and a history of congenital long QT syndrome, or torsades de pointes).
19. Receiving or requiring the continued use of medications that are known to be strong or moderate inhibitors and inducers of CYP3A4/5 and strong Pgp inhibitors. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and Pgp inhibitors) before receiving a dose of TAK-981.
20. Female patients who are lactating and breastfeeding or have a positive urine or serum pregnancy test during the screening period or on Day 1 before first dose of study drug.
21. Patients in Germany who are committed to an institution by virtue of an order issued either by judicial or administrative authorities as per German law.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). All patients will receive TAK-981 and rituximab as specified in the schedule of events (SOEs) (Appendix A).

Each 21-day treatment cycle will consist of TAK-981 administration on Day 1 and Day 8 (2 weeks on and 1 week off) or on Days 1, 4, 8, and 11 (BIW) every 21 days as per the assigned cohort. During Cycle 1 only, rituximab will be dosed in a loading regimen that consists of rituximab at the clinically approved dose of 375 mg/m^2 on Days 1, 8, and 15 of a 21-day cycle. From Cycle 2 onwards, TAK-981 will be administered as per the assigned schedule, ie, Days 1 and 8 or Days 1, 4, 8, and 11, and rituximab only on Day 1 of each 21-day cycle. During Phase 1 of this study, alternative dosing schedules for TAK-981 (eg, Day 1, or Days 1, 4, 8, and 11, or Days 1, 8, and 15 in 21-day cycles) were explored, only after discussions between sponsor and the investigators. For

patients initially treated with TAK-981 in a more dense schedule, such as on Days 1, 4, 8, and 11 or Days 1, 8, and 15 for at least 6 cycles; and that present with an objective response, a less dense schedule of TAK-981 (eg, on Day 1, or on Days 1 and 8) may be considered upon discussion and agreement between the investigator and sponsor.

On C1D1 only, rituximab will be administered first (before TAK-981 infusion). Starting at C1D8 onwards, TAK-981 will be administered before rituximab on days on which both TAK-981 and rituximab are given on the same visit day. At least 1 hour should elapse between the completion of the infusion of the first study drug and the initiation of the infusion of the second study drug.

The rationale for dosing rituximab before TAK-981 on C1D1 is that most of the infusion reactions due to rituximab in patients have been reported primarily during the first infusion with time to onset of 30 to 120 minutes (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019). The proportion of patients experiencing acute IRRs decreases with subsequent courses of rituximab (van Vollenhoven et al. 2010; van Vollenhoven et al. 2015). Although most rituximab-related reactions are mild to moderate in severity, there is a theoretical risk that when combined with TAK-981 any such reactions could be more severe. Therefore, rituximab is administered after premedication and before TAK-981 infusion on C1D1. Subsequent rituximab infusions are administered after TAK-981 infusion to facilitate PK/pharmacodynamic sampling.

Should no Grade 3 or greater IRR be observed at the PAD or MTD, the SMC may determine that TAK-981 be administered before the rituximab infusion on C1D1 of subsequent patients enrolled in the study.

Note: Fever is a common TEAE associated with the TAK-981 infusion. Consider prescribing postinfusion antipyretic medications for up to 24 hours after the end of the TAK-981 infusion as a preventative measure. For any patient that has an infusion related fever, consider premedication with an antipyretic medication as prophylaxis. Investigator may consider reducing, even discontinuing, predose and postdose antipyretics if the patient experiences no major infusion-related fever. The clinical site is responsible for sourcing any pre- and post-medications outlined in the protocol.

8.1.1 Rituximab

Rituximab is available as single-use vials of 100 mg/10 mL and 500 mg/50 mL of drug substance (refer to Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).

The dose of rituximab will be calculated based on actual weight at enrollment. The total doses of rituximab throughout therapy should be based on the pretreatment body surface area (BSA) calculated using the Du Bois formula ($BSA = 0.007184 \times Weight^{0.425} \times Height^{0.725}$) without consideration of fluctuations in body weight during treatment. Dose escalations or dose reductions of rituximab are not allowed in this study.

Premedication with an antihistamine and acetaminophen is required before rituximab dosing, in accordance with local best practice.

The first rituximab infusion (C1D1), will be initiated at a rate of 50 mg/hour and the infusion rate will be increased by 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour in the

absence of IRR. If no IRR happened in the previous infusion, subsequent administrations can be initiated at 100 mg/hour with 100 mg/hour increments every 30-minute interval to a maximum of 400 mg/hour and in the absence of IRR. Starting at Cycle 2, if the patient did not experience Grade 3 or 4 IRR in Cycle 1, a 90-minutes infusion can be used at investigator's discretion. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms resolve.

8.1.2 TAK-981

TAK-981 will be provided as a Solution for Infusion containing 10 mg/mL TAK-981 drug substance (refer to the pharmacy manual).

The TAK-981 dose for each dose level in Phase 1 and for Phase 2 will be decided by the SMC at each End of Cohort meeting. TAK-981 will be administered as a 60 ±10 minute IV infusion. If infusion reactions are observed, the length of the infusion can be extended up to 2 hours for all patients without requiring a protocol amendment.

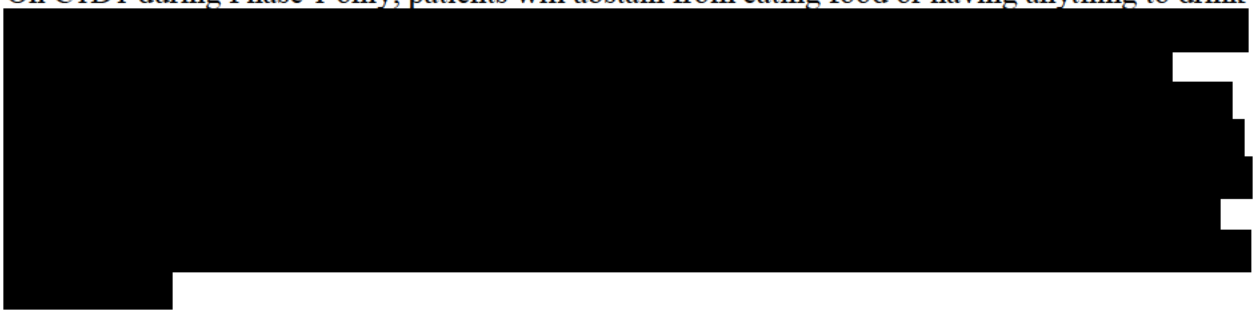
During dose escalation, the first 3 patients at a given dose level will be hospitalized for C1D1 for drug administration and observation for a minimum of 18 hours after the end of infusion of TAK-981. For subsequent patients enrolled at the same dose level, hospitalization will not be required if the risk of IRRs and/or CRS is considered to be low by the SMC.

Patients can be discharged after the 18-hour observation period only if there are no signs and symptoms of acute toxicity like fever, significant changes in blood pressure and/or heart rate. Patients who experience any treatment-related AEs during the 18-hour observation period should be further monitored as clinically indicated. If no infusion reaction is observed in C1D1, subsequent treatment for that patient can be administered in an outpatient setting.

Patients will be asked to maintain adequate hydration (1.5-2 L/day) 48 hours before initiating therapy and during C1D1, and IV fluid administration on C1D1 is recommended for those who cannot maintain adequate oral hydration. Investigator may consider reducing, even discontinuing, predose and postdose antipyretics if the patient experiences no major infusion-related fever.

8.1.3 Additional Instructions for Treatment Administration

On C1D1 during Phase 1 only, patients will abstain from eating food or having anything to drink



Vital signs will be monitored throughout study drug administration according to the SOE (Appendix A). All patients will be monitored for 2 hours after the end of infusion of the last study drug. After the administration of TAK-981 or rituximab, the patient should be considered clinically stable by the investigator or designee before the next study drug is administered or the patient is discharged. If no infusion reaction is observed in the first 2 cycles, postinfusion monitoring may not be required and the patient can be discharged from the site per investigator discretion.

In all cases, the administration of TAK-981 or rituximab should occur in an area with access to resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Treatment must be stopped if the patient experience symptoms compatible with an infusion reaction of Grade 2 or greater. The management of infusion reactions and CRS is detailed in Section 8.10.6 and Section 8.10.7.

Dose administration of TAK-981 and rituximab should be performed on schedule; however, a dose delay of up to 4 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor (see Section 8.8). For patients in the DLT-evaluation period (Cycle 1) rescheduling is allowed for a maximum of 1 dose. At least 7 days should elapse between consecutive doses of rituximab. On days on which both TAK-981 and rituximab are administered, should the treatment day be rescheduled, both TAK-981 and rituximab doses will be rescheduled.

As with other potentially toxic compounds, caution should be exercised in handling this drug. The use of gloves is recommended. Following topical exposure, events could include redness or blistering. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Administration through a central port is always preferred versus a peripheral line.

8.2 Definitions of DLT for Phase 1 Only

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0; except CRS, which will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). During the Phase 1 part of the study, a DLT will be defined as any of the following AEs that occur during Cycle 1 unless they are considered by the investigator to be clearly unrelated to therapy:

1. Any Grade 5 AE.
2. Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) lasting ≥7 consecutive days.
3. Febrile neutropenia: Grade ≥3 neutropenia (ANC $<1 \times 10^9$/L) with fever and/or infection, where fever is defined as a single temperature >38.3°C or sustained temperature of ≥38°C for more than 1 hour.
4. Grade 4 thrombocytopenia lasting ≥7 consecutive days.
5. Grade 3 thrombocytopenia lasting ≥14 days or accompanied by ≥Grade 2 bleeding.
6. A platelet count <10,000/mm^3 at any time.

7. Grade ≥3 nonhematologic toxicity with the following exceptions:
    - Grade 3 fatigue lasting less than 7 days.
    - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs within 1 week.
    - Grade 3 endocrine disorder that is managed with or without therapy and the patient is asymptomatic.
    - Grade 3 or 4 inflammatory reaction attributed to a local antitumor response.
    - Grade 3 IRR that resolves within 6 hours with appropriate clinical management.
    - Nonhematological laboratory changes that are otherwise asymptomatic and that can be controlled to ≤Grade 1 or baseline in 7 days with appropriate treatment or with dose interruption, and does not result in a delay of >7 days of planned treatment. In this setting, a course of action will be determined jointly by the investigators and the sponsor clinician.
    - Grade 3 elevation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤Grade 2 with supportive care within 7 days and is not associated with other clinically significant consequences.
    - Isolated Grade 3 electrolyte abnormalities that resolve to ≤Grade 2 with supportive care within 7 days and are not associated with other clinically significant consequences.
    - Grade 3 TLS or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤Grade 2 within 7 days.
    - ≥Grade 3 diarrhea that can be controlled to ≤Grade 1 or baseline in 7 days with optimal supportive therapy.
    - ≥Grade 3 nausea and/or emesis that can be controlled to ≤Grade 1 or baseline in 7 days with the use of optimal antiemetics (defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules).
    - Grade 3 rash lasting ≤7 days after treatment that includes topical steroid treatment, oral administration of antihistamines, and pulse oral steroids (if necessary).
8. Delay in the initiation of Cycle 2 by more than 14 days from the scheduled Cycle 2 Day 1 date due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
9. Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug and dose-limiting.

DLTs for dose-escalation purposes will be evaluated during Cycle 1. Although DLT-like events may occur at any point during treatment, only DLTs observed during the DLT-evaluation period (Cycle 1) will necessarily influence dose-escalation decisions and MTD determination per BLRM. While the primary escalation schema is designed to determine MTD based on DLTs during its

evaluation period, cumulative toxicity beyond the DLT-evaluation period will be considered in assessing the overall tolerability of a given dose and consequently influence the dose escalation decision and selection of the RP2D. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

Patients experiencing a DLT may continue in the study if they are deriving clinical benefit upon agreement by the sponsor, but they will be administered reduced doses of TAK-981 as appropriate.

8.3 Definition of DLT-Evaluable Patients for Phase 1 Only

Patients assigned to a particular dose cohort in Phase 1 are considered evaluable for assessment of a DLT if either of the following criteria are met during the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of TAK-981.

  OR

- The patient completed all planned infusions of TAK-981 and 3 infusions of rituximab.

For the Phase 1 part of the study, patients who withdraw before completing the 3-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

8.4 Definition of PAD

The PAD of TAK-981 is defined as the dose at which there is evidence of pharmacodynamic effects (which may include the induction of cytokines/chemokines or type 1 IFN signature in blood, or evidence of activation of immune cells or antitumor activity). The PAD can be defined retrospectively once MTD is reached and it can be below MTD or coincide with it.

8.5 Dose-Escalation Rules for Phase 1 Only

In the Phase 1 portion of the study, only TAK-981 will be escalated. Rituximab is administered at a fixed dose of 375 mg/m^2 for each scheduled infusion. The following dose levels of TAK-981 are considered a priori:10, 15, 25, 40, 60, 90, 120, and 160 mg. Evaluation of intermediate doses, and expansion of an existing dose level 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 relationships between dose and toxicity, exposure, or pharmacodynamics.

Initially, a minimum of 3 patients will be enrolled at the starting dose level. A provision of cohorts of 4 patients is contemplated during dose escalation to have an extra patient in case 1 of the 3 earlier patients is unevaluable, or, if a patient within the cohort experiences a DLT, requiring cohort expansion to 6 patients. The following rules will be used only for this initial dose level:

- If none of the 3 patients experiences a DLT during the first cycle, the dose may be escalated for the next planned dose level.

- If 1 of the 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
  - If no more than 1 patient out of the 6 total patients has a Cycle 1 DLT, 3 patients will be enrolled at the next dose level.
  - If 3 or more of the 6 patients experience a Cycle 1 DLT, the starting dose level will be considered not tolerated and the dose will be de-escalated to 1 mg.
  - If 2 of the 6 patients have a Cycle 1 DLT, 3 additional patients will be enrolled. If any of those 3 additional patients have a Cycle 1 DLT, the starting dose will be considered not tolerated and dose will be de-escalated to 1 mg. If none of the 3 additional patients have a Cycle 1 DLT, the starting dose may be considered the MTD or escalated to the next dose level along with consideration of other safety, clinical, PK, and pharmacodynamic data.
- If 2 or more patients of the 3 patients exhibit a DLT, then the starting dose level is considered too toxic, and the dose will be de-escalated to the 1 mg dose.

Alternative dosing schedules for TAK-981 (eg, Day 1, or Days 1, 4, 8, and 11, or Days 1, 8, and 15) may be explored in agreement between the investigators and sponsor. TAK-981 escalation for different TAK-981 schedules will be evaluated separately.

Dose-escalation and cohort expansion decisions will be determined by the SMC. The SMC will review the Cycle 1 safety of all treated patients and make decisions regarding dose escalation. In addition, the available PK and pharmacodynamic information from this study as well as emerging safety, PK, and pharmacodynamic data from the FIH study (TAK-981-1002) will be evaluated to support the dose-escalation decisions by the SMC.

Starting from the second dose of patients, the BLRM will be used for dose recommendations as well as information from the FIH study TAK-981-1002. However, at the End of Cohort meeting the SMC will make the final decision on the next dose level based on the evaluation of all evidence available. The recommended dose by BLRM will be the one that has the highest posterior probability of having a DLT rate that falls into the interval [0.16, 0.33]. In the meantime, following the Escalation With Overdose Control principle, the posterior probability of the recommended dose having a DLT rate above 0.33 must not exceed 35% (see Section 13.3 and Appendix H). Escalation may continue until 1 of the following stopping rules is met:

> At least 6 patients are enrolled at the current dose and the current dose is the recommended dose for the next cohort,
>
> *OR*
>
> At least 9 patients are enrolled at the next recommended dose level and the posterior probability of the next recommended dose level having a DLT rate that falls into the interval [0.16, 0.33] exceeds 50%.

Once either of the above rules has been met, MTD may be declared. The study team may decide to stop dose escalation without identifying MTD based on pharmacodynamic markers, antitumor activity, non-DLT AEs, PK, or a combination of all or some of these factors. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level 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, exposure, or pharmacodynamics of TAK-981.

8.6 Dose Management and Modification Guidelines

Patients will be evaluated according to the SOE (Appendix A) for possible toxicities. Toxicities are to be assessed according to the NCI CTCAE Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019).The causal relationship of each AE should be assessed in relation to TAK-981 and to rituximab so that dose modifications can be made accordingly.

Dose management and modification guidelines for toxicities are described below for TAK-981 based on the nature and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor clinician (or designee). In this study the dose of rituximab cannot be modified. Depending on the toxicity observed the infusion of rituximab can be interrupted (in case of IRR, for example), delayed, or discontinued.

8.6.1 Intrapatient Dose Escalation

Patients who have tolerated treatment at the initially assigned dose may have their doses of TAK-981 increased in subsequent cycles of treatment only if all patients in the next dose level cohort have completed assessment for Cycle 1 and a decision has been made that this dose level does not exceed the MTD.

8.6.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

A treatment cycle in this study is 21 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC $\geq 1.0 \times 10^9$/L.
- Platelet count $\geq 75.0 \times 10^9$/L (platelet count $\geq 50.0 \times 10^9$/L if no change on the baseline platelets level from the screening visit and it is clearly due to marrow involvement).

Before starting a new treatment cycle, TAK-981/rituximab-related AEs or laboratory abnormalities must have returned to ≤Grade 1 or baseline (unless otherwise specified). If the patient fails to meet the criteria cited above for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor.

8.6.3 Criteria for Dose Interruption or Dose Reduction

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-981,

rituximab, or the combination may continue study treatment with the same dose, may have the treatment held or may be permanently discontinued from the study. Patients who have study drugs held because of treatment-related or possibly related AEs should resume study drug treatment according to the dose modification guidelines below.

8.6.3.1 TAK-981

Dosing of TAK-981 should be interrupted during a treatment cycle or reduced according to the dose modification recommendations listed in Table 8.a for nonhematologic toxicity and Table 8.b for hematologic toxicities. When the dose of TAK-981 is withheld based on the listed criteria, clinical and laboratory reevaluation should be repeated at QW or more frequently, depending on the nature of the toxicity observed until the toxicity resolves to the Grade specified in Table 8.a and Table 8.b. If indicated, TAK-981 dose should be reduced by at least 1 dose level (or by 50% if the patient is receiving the first dose level).

If TAK-981 alone or in combination with rituximab cannot be administered within a cycle in a 48-hour window, because of an AE, the dose will be missed and the patient will be scheduled for the next administration per SOE.

In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, or there were other circumstances contributing to the AE that are unlikely to recur, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-981 due to AEs are permitted. If more than 2 dose-level reductions of TAK-981 are needed to manage TAK-981 related AEs, treatment with TAK-981 should be discontinued.

In the Phase 1 portion of the study, intrapatient dose reductions of TAK-981 are not permitted in Cycle 1 unless the patient experiences a DLT attributed to TAK-981. DLTs are defined in Section 8.2. Patients experiencing a DLT in Cycle 1 may continue in the study upon resolution of the toxicity; however, a dose reduction by at least 1 dose level of TAK-981 should be considered based on the toxicity and discussion between investigator and sponsor.

Refer to the Pharmacy manual for dose level reduction table.

Table 8.a General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Treat according to local practice. Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to ≤Grade 1 or baseline and then restarted at the same dose or, depending on the toxicity, resume treatment at the next lower dose level.
Grade 3 and Grade 4 non – life-threatening AEs	Hold TAK-981 until resolution to ≤Grade 1 or baseline, and then resume treatment at the next lower dose level, except for the following instances that do not require dose reduction: • ≥Grade 3 nausea, vomiting, and/or diarrhea resolved to ≤Grade 1 or baseline within 72 hours with optimal antiemetics and/or antidiarrheal following local practice. • Transient Grade 3 fatigue (lasting <72 hours) and asymptomatic ≤Grade 4 laboratory abnormalities that the investigator considers not clinically significant following agreement between sponsor and investigators. – *Note: for QTcF ≥501 ms or >60 ms change from baseline, consult a cardiologist, manage according to standard clinical practice. For Grade 3 events treatment withdrawal should be evaluated; discuss with Takeda/designee. For Grade 4 events, study drug should be permanently discontinued (oncologypro.esmo.org/education-library/esmo-handbooks/oncological-emergencies/introduction, Chapter 1: Cardiac Complications of Cancer and Anticancer Treatment, in ESMO Handbook of Oncological Emergencies, Accessed 22 April 2022).
Grade 4 life-threatening AEs	Permanently withdraw the patient from the study.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or ≤Grade 1 or if considered a sequela), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment should be resumed at a reduced dose level after resolution of AEs to ≤Grade 1 or baseline.

AE: adverse event; CRS: cytokine release syndrome; QTcF: QT interval with Fridericia correction method.
For specific instructions in case of CRS, consult Section 8.10.7.

Table 8.b Dose Adjustments for TAK-981 Hematologic Drug-Related AEs

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN-1.5 × 10^9 cells/L).	Continue TAK-981 at the same dose level.
Grade 2 (ANC 1.0- <1.5 × 10^9 cells/L).	Continue TAK-981 at the same dose level.
Grade 3 (ANC 0.5- <1 × 10^9 cells/L) without fever.	Withhold dose until resolved to ≤Grade 2 or baseline, then: If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, resume treatment at the previous safe lower dose level (ie, reduce by 1 dose level).
Grade 4 (ANC <0.5 × 10^9 cells/L) without fever.	Withhold dose until resolved to ≤Grade 2 or baseline, then if resolved in ≤7 days, resume treatment at the same dose level. If recovered in >7 days, second Grade 4 neutropenia event, ANC >0.1 × 10^9/L, or concomitant occurrence of mucositis or thrombocytopenia, resume treatment at the previous safe dose level.
Febrile neutropenia (ANC <1.0 × 10^9 cells/L, with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than 1 hour).	Withhold dose until fever/infection have recovered and ANC ≤Grade 2 or baseline, then resume treatment at the previous safe lower dose level (ie, reduce by 1 dose level).
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN-75.0 10^9 cells/L)	Continue TAK-981 at the same dose level.
Grade 2 (PLT <75.0 – 50.0 × 10^9 cells/L)	Continue TAK-981 at the same dose level.
Grade 3 (PLT <50.0 – 25.0 × 10^9 cells/L) without bleeding.	Withhold dose until resolved to ≤Grade 1 or baseline, then: If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, resume treatment at the previous safe lower dose level (ie, reduce by 1 dose level).
Grade 4 (PLT <25.0 × 10^9 cells/L) without bleeding.	Withhold dose until resolved to ≤Grade 1 or baseline, then if resolved in ≤7 days, resume treatment at the same dose level, if resolved in >7 days, then resume treatment at the previous safe lower dose level.
PLTs <10.0 × 10^9 cells/L, thrombocytopenia ≥Grade 3 associated clinically significant bleeding, second event of Grade 4 thrombocytopenia >7 days.	Consider permanently withdrawing the patient from the study, except when there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. In this case, treatment should be resumed at a reduced dose level after resolution of AEs to ≤Grade 1 or baseline.

AE: adverse event; ANC: absolute neutrophil count; LLN: lower limit of normal; PLT: platelet.

Observation of isolated Grade 3/4 lymphopenia during Cycle 1 is not sufficient to hold the administration of TAK-981.

Table 8.c TAK-981 Dose Modification Guidelines for CRS

ASTCT Consensus Grade	TAK-981 Dose Modification
Grade 1: Fever [a] (≥38°C)	Continue TAK-981 at the same dose.
Grade 2: Fever [a] (≥38°C) with hypotension not requiring vasopressors; and/or [b] hypoxia requiring low-flow [c] nasal cannula	Withhold dose until resolved to ≤Grade 1, then: • If resolved in ≤14 days, maintain dose level. • If resolved in >14 days or repeat event, reduce by 1 dose level. • If >2 consecutive doses of TAK-981 are skipped due to CRS, permanently discontinue treatment with TAK-981.
Grade 3: Fever [a] (≥38°C) with hypotension requiring a vasopressor with or without vasopressin; and/or [b] hypoxia requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask	Withhold dose until resolved to ≤Grade 1, then: • If resolved in ≤14 days, reduce by 1 dose level and if toxicity does not recur, consider re-escalating to original dose level. • If resolved in >14 days or repeat event, reduce by 1 dose level. • If >2 consecutive doses of TAK-981 are skipped due to CRS, permanently discontinue treatment with TAK-981.
Grade 4: Fever [a] (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin); and/or [b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Permanently discontinue TAK-981.

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome.

ASTCT consensus grade adapted from Lee et. Al. 2019 (Lee et al. 2019); CRS management recommendations are adapted from Neelapu et al, 2018 (Neelapu et al. 2018) and should be implemented at the investigator's discretion.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

8.6.3.2 Rituximab

In this study the dose of rituximab cannot be modified. Depending on the toxicity observed the infusion of rituximab can be interrupted (in case of IRR, for example), delayed, or discontinued. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted, but dose modifications are not allowed. The patient should be treated according to the

appropriate standard of care. Patients who discontinue rituximab for reasons described in Appendix I (Rituxan (rituximab) Injection for Intravenous Use 2019) may continue TAK-981 treatment.

8.6.3.3 COVID-19 Infection

If a patient is diagnosed with COVID-19 infection while on study, study treatment must be withheld until resolution of the infection. A patient may restart study treatment if the following criteria are met; otherwise the patient must discontinue treatment:

- The infection must have resolved without ongoing clinical sequalae.
- There should be 2 sequential negative severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) tests 12 hours apart. Discuss with sponsor if needed considering polymerase chain reaction tests may continue to be positive for a prolonged period of time (Qu et al. 2020) (Plebani 2021) (cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html, Center for Disease Control. Ending Isolation and Precautions for People with COVID-19: Interim Guidance. Updated 14 January 2022. Accessed 22 April 2022).
- The patient must be asymptomatic and the investigator believes, with agreement of the sponsor, that the patient would benefit from resuming study treatment.

8.6.4 Criteria for Discontinuation of Study Treatment Due to AEs

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

- Occurrence of a DLT in dose escalation during the first cycle (exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit and risk assessment).
- Occurrence of drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.6 and the rituximab United States Package Insert (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).
- If subsequent cycle is delayed by >14 days for treatment-related AEs despite supportive treatment per standard clinical practice. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit-risk assessment.)
- If more than 2 dose reductions of TAK-981 are required for a patient. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit-risk assessment.)
- Occurrence of AEs, resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the patient (if applicable).

It is possible that rituximab is permanently discontinued due to drug-related AEs, while the patient continues to receive TAK-981 and remains on treatment. Discontinuation of treatment occurs only

when TAK-981 is required to be discontinued due to AEs or upon the occurrence of any of the other non-AE criteria.

If TAK-981 treatment discontinuation is determined, the EOT visit should be completed within 30 (+10) days of the last administration of TAK-981 alone or the combination and before the start of subsequent anticancer therapy.

8.7 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study (In Phase 2, if medications are needed for optimal patient management, discuss with sponsor):

- Any investigational agent other than TAK-981.
- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy and once PD is ruled out), or standard or investigational agents for treatment of cancer.
- Concomitant corticosteroid administration of >20 mg of prednisone or equivalent unless given as treatment or prophylaxis for IRRs, as premedication for administration of certain blood products (80 mg methylprednisolone is accepted) or short courses (<48 hours) for exacerbations of respiratory tract disorders or for acute control of emerging tumor pain.
- Strong and moderate CYP3A4/5 inhibitors and inducers (see list in Appendix E). During the study, should patients require the use of medications that are known to be strong and moderate inhibitors/inducers of CYP3A4/5, they should temporarily discontinue the use of TAK-981. These patients can resume treatment with TAK-981 approximately 1 week after discontinuing the use of these strong and moderate inhibitors CYP3A4/5, and approximately 2 weeks after discontinuing the use of strong and moderate inducers of CYP3A4/5.
- Strong inhibitors of Pgp (see list in Appendix F).
- Because the safety of immunization with live viral vaccines following rituximab therapy has not been studied, vaccination with live virus vaccines is not recommended while the patient is being treated on study (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).
- For patients enrolled in Phase 1, vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs.
- During Phase 1, on C1D1, the initiation of therapy with drugs that are known to prolong the QTc interval. [redacted]

8.8 Permitted Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first study drug administration through the EOT visit or before initiation of new anticancer therapy (whichever comes first) will be recorded in the designated electronic case

report form (eCRF). Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are permitted while the patient is receiving the study drug:

- Myeloid growth factors (eg, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) and/or erythropoietin support as clinically indicated are permitted.
- Topical or inhaled steroids (eg, for the treatment of asthma) are permitted.
- Patients should be transfused with RBCs and platelets as clinically indicated.
- Concomitant treatment with bisphosphonates or RANKL inhibitors will be allowed for patients with evidence of lytic destruction of bone or with osteopenia, according to the American Society of Clinical Oncology Clinical Practice guidelines or institutional practice in accordance with the product label, unless specifically contraindicated.
- Narrow therapeutic range Pgp substrates such as digoxin or dabigatran may be used with caution, and patients requiring use of these drugs will be closely monitored.
- COVID-19 vaccination is generally allowed for patients enrolled in the study with the exception of live attenuated vaccines which must be completed at least 4 weeks prior to treatment initiation. COVID-19 vaccination should follow local guidance and regulations. Ideally, patients will have completed vaccination prior to treatment initiation as treatment with rituximab may negatively affect the efficacy of vaccination. For patients enrolled in Phase 1, vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs. Vaccination should be avoided within ± 3 days of TAK-981 administration and should be administered after the last dose of TAK-981 of a given cycle; study treatment may be delayed for up to 7 days to accommodate a vaccine dose administration after discussion with the Sponsor. Vaccination should be captured as a concomitant medication.

Additional concomitant medications and procedures are permitted during the study to prevent and actively manage AEs related or not related to the study drug(s) unless prohibited as specified in the protocol. Supportive measures consistent with optimal patient care may be given throughout the study unless prohibited as specified in the protocol.

8.9 Precautions and Restrictions

Precautions and requirements for a safe administration of TAK-981 and/or rituximab are detailed in Section 8.1.

It is not known what effects TAK-981 or rituximab has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception

through defined periods during and after study treatment as specified below (see also Appendix J for acceptable methods of contraception).

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

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 1 year after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

Before starting treatment, male patients should be advised to seek counseling on sperm storage, and female patients should be advised to seek counseling on egg storage.

8.10 Management of 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, granulocyte colony-stimulating factor, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology/American Society of Clinical Oncology guidelines or local institutional practice. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.6.

In the sections below guidance for the management of some expected AEs based on observations in nonclinical toxicology or other AEs that have not been substantiated in these experiments but that could be expected because of the mechanism of action of TAK-981, and warnings and precautions in the rituximab label. This guidance is not expected to replace investigator judgment in the management of AEs. Additional information on the potential risks can be found in Sections 4.2.5 and 4.5.1, and the current IB.

8.10.1 Nausea or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea or vomiting will be actively managed by employing optimal antiemetic treatment 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-hydroxytryptamine 3 serotonin receptor antagonist and a short course of corticosteroid given in standard doses and according to standard schedules. If these are inadequate, an NK-1 antagonist may be added.

8.10.2 Diarrhea

This study will not initially employ prophylactic antidiarrheals; however, there is no prophibition against their use in the management of a patient who develops diarrhea. Patients will be instructed to take antidiarrheal medication(s) (ie, loperamide) at the physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

8.10.3 Anemia, Thrombocytopenia, or Neutropenia

Please refer to Table 8.b for dose delay and reduction recommendations for hematologic toxicities. TAK-981 should be held if a significant treatment-emergent cytopenia or bleeding is suspected to be related to, or can be worsened by, study treatment. Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBCs or platelet) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/thrombocytopenia at the discretion of the investigator per standard clinical practice. Use of myeloid growth factor (eg, granulocyte colony-stimulating factor) support to treat ≥Grade 3 neutropenia and/or febrile neutropenia is recommended per regional guidelines or local institutional practice; prophylaxis is permitted per regional guidelines or local institutional practice.

8.10.4 Infusion Site Care

Skin lesions, which may include inflammation or necrosis, represent a potential risk of TAK-981 and were observed at the injection site in rats. Local institutional guidelines must be applied to stress proper administration and prevention of accidental extravasation of TAK-981. Usage of IV port is highly recommended. IV line should be flushed at the end of the infusion accordingly to local procedures. Monitoring at the beginning and during infusion must be ensured. If extravasation occurs, the infusion must be discontinued immediately and institutional guidelines applied. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. Patients should be instructed to report any discomfort, pain, or swelling at the infusion site.

8.10.5 Lymphopenia and Opportunistic Infection Prophylaxis

Because lymphopenia is one of the most common AEs associated with the use of rituximab and is also an expected TAK-981–related AE, patients may be at an increased risk of opportunistic pathogens. Follow-up with standard hemograms and serial immunophenotyping will help to make clinical decisions about the risk of immunosuppression.

Prophylaxis for *Pneumocystis jiroveci* pneumonia should be initiated 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.

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.

In the event of long-lasting lymphopenia, pneumocystis, or herpes zoster infection, prophylaxis can be started at investigator's discretion.

8.10.6 IRRs

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Premedication with an antihistamine and acetaminophen is required before rituximab dosing, in accordance with local best practices. Should infusion-related events develop during rituximab infusion, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms resolve. If, in accordance with local clinical guidelines, a 90-minute rituximab infusion is given and the patient experiences an infusion reaction, refer to local prescribing information for infusion adjustments (Appendix I) (Rituxan (rituximab) Injection for Intravenous Use 2019).

Although TAK-981 is not a biological drug, its immune activating properties may also produce AEs in the category of IRRs. If such reactions were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines as appropriate. If an IRR develops during the TAK-981 infusion, the patient should be closely monitored until recovery of symptoms. The patient will be permanently discontinued from the study in case of a Grade 4 life-threatening reaction. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and communicated as an SAE if criteria are met. Concomitant medications administered for infusion

reaction treatment should be collected in the eCRF. Investigator may consider reducing, even discontinuing, predose and postdose antipyretics if the patient experiences no major infusion-related fever. If a patient presents signs and symptoms compatible with infusion reaction on days on which just TAK-981 is given, and at investigator discretion, premedication can be instituted for the remaining TAK-981 doses.

8.10.7 CRS

CRS should be diagnosed and managed following institutional guidelines and graded following ASTCT Consensus Grading for CRS (Lee et al. 2019). Recommendations for management of CRS are shown in Table 8.d and can be implemented at the investigator's discretion. Please refer to Table 8.c for dose modifications after a CRS event.

Table 8.d CRS Management Recommendations

ASTCT Consensus Grade	CRS Management Recommendations
Grade 1: Fever [a] (≥38°C)	Monitor fluid status. Supportive care: antipyretics, analgesics.
Grade 2: Fever [a] (≥38°C) with hypotension not requiring vasopressors; and/or [b] hypoxia requiring low-flow [c] nasal cannula	As per Grade 1 and: • Closely monitor all organ functions, including cardiac function. • IV fluid bolus. • Supportive care.
Grade 3: Fever [a] (≥38°C) with hypotension requiring a vasopressor with or without vasopressin; and/or [b] hypoxia requiring high-flow [c] nasal cannula, facemask, nonrebreather mask, or Venturi mask	As Grade 2 and: • Closely monitor all organ functions, including cardiac function. • Tocilizumab (8 mg/kg IV; maximum dose 800 mg) can be repeated after 6 hours. • If refractory to tocilizumab, dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg every 6 hours or equivalent methylprednisone. • Vasopressors as needed. • Supplemental oxygen as needed for hypoxia (including high-flow O_2 and CPAP). • Transfer to ICU.
Grade 4: Fever [a] (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin); and/or [b] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	As per Grade 3 and: • Substitute dexamethasone with methylprednisone 1 g IV per day. • Mechanical ventilation.

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; ICU: intensive care unit; IV: intravenous; O_2: supplemental oxygen.

ASTCT consensus grade adapted from Lee et. Al. 2019 (Lee et al. 2019); CRS management recommendations are adapted from Neelapu et al, 2018 (Neelapu et al. 2018) and should be implemented at the investigator's discretion.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS, then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

8.10.8 TLS

Rituximab rapidly decreases the number of benign and malignant CD20+ cells, which can result in TLS (as defined in Appendix L). TLS has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with NHL. The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumor burden are at greater risk of TLS. Reduced renal function further increases the risk.

Tumor burden assessments, including radiographic evaluation (eg, CT scan) should be performed at screening as well as blood chemistry assessments (creatinine, uric acid, potassium, phosphorus, calcium, albumin, and corrected calcium, if available) in all patients. Preexisting abnormalities should be corrected before initiation of treatment.

During C1D1, the prophylaxis measures listed below should be followed and more intensive measures (including hospitalization) should be employed as overall risk increases:

Hydration: Ensure adequate hydration (1.5-2 L) 48 hours before initiating therapy. Administer IV fluids as indicated based on overall risk of TLS or for those who cannot maintain adequate oral hydration.

Antihyperuricemic agents: Consider administration of allopurinol 72 hours before initiation. Rasburicase is recommended for patients at high-risk, especially those with high tumor burden.

Laboratory Assessments:

Predose: Assess blood chemistries before initiating treatment to evaluate kidney function and correct preexisting abnormalities.

Postdose: Monitor blood chemistries at 6 to 8 hours and at 24 hours after the rituximab dose. In Phase 2, the 24 hour sample is not required but may be collected based on the physician's assessment of the patient's TLS risk. Electrolyte abnormalities should be corrected. For hospitalized patients due to high-risk TLS, monitor blood chemistries at 4, 8, 12, and 24 hours, and, as needed, after the rituximab dose.

Hospitalization: Based on investigator assessment, patients with high tumor burden (at least 1 lesion >10 cm; or at least 1 lesion >5 cm and circulating lymphocytes >25,000 cells/mm^3) and/or creatinine clearance <60 mL/min, are at greater risk of TLS and hospitalization should be considered for the first 24 to 48 hours of treatment for more intensive prophylaxis and monitoring. Consider hospitalization for subsequent doses based on reassessment of risk.

Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as clinically indicated.

8.11 Blinding and Unblinding

This is an open-label study.

8.12 Description of Investigational Agents

TAK-981

TAK-981 drug product has been developed as an injection, for IV use (solution for infusion). [redacted] It is packaged in a glass vial containing 10 mL of TAK-981 sterile solution, with 0.5 mL excess volume.

For specific information about the storage and handling of TAK-981 drug product, refer to the study or pharmacy manual associated with a given study protocol or the Instructions for Use contained in the shipping package.

Full details are available in the IB.

Rituximab

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5. Full details are available in Appendix I (Rituxan (rituximab) Injection for Intravenous Use 2019).

8.13 Preparation, Reconstitution, and Dispensation

TAK-981

The reconstituted product will be administered by IV infusion over 1 hour (±10 minutes). After the end of the infusion the IV line should be flushed accordingly to local standards. Detailed reconstitution and dosage preparation instructions are provided in the Directions for Use located in the pharmacy manual.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

TAK-981 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-981.

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

Rituximab

Rituximab will be administered IV at the clinically approved dose of 375 mg/m^2. The dose of rituximab will be calculated based on actual weight at enrollment (using weight obtained either at screening or on Day 1) and remains constant throughout the study. Reconstitution and dosage preparation instructions should be applied as indicated in the drug label.

Commercially available IV formulation of rituximab background therapy will be used. The Sponsor will provide commercial supplies of rituximab for IV administration, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Subjects enrolled in countries where rituximab is designated as non-investigational product, should obtain commercially available product through the local hospital pharmacy or licensed distributor. Subjects enrolled in countries where rituximab is designated as investigational product, will have rituximab supplied and packaged by the sponsor.

8.14 Packaging and Labeling

All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.15 Storage, Handling, and Accountability

TAK-981

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained for all used and unused study drug vials. A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients will be provided and kept at the study site. Disposal instructions are provided in the pharmacy manual.

The required storage condition for TAK-981 study drug is -20°C ± 5°C. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-981 received and that any discrepancies are reported and resolved before use of TAK-981.

Rituximab

Rituximab vials (100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials) are stable at 2°C to 8°C (36°F to 46°F). Rituximab vials should be protected from direct sunlight. Diluted rituximab solution should be stored at 2°C to 8°C because there is no preservative. The diluted solution is stable for 24 hours at 2°C to 8°C.

8.16 Other Protocol-Specified Materials

Information on supplies required by the site for drug administration is provided in the pharmacy manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the study manual.

9.0 STUDY CONDUCT

This study 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 project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator, and other vendors such as the interactive response technology provider, may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

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

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB. Prisoners (or other populations that might be subject to coercion or exploitation) will not be enrolled into this study.

9.3 Treatment Group Assignments

This is not a randomized study. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study. Details can be found in the cohort management plan.

9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, treatment, EOT, follow-up, and end of study. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of the study drug. Procedures conducted during the screening period that are performed within 3 days of C1D1 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 drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. The timing of PK and pharmacodynamics assessment is specified in the SOE (Appendix A). Laboratory assessments may occur up to 3 days before the scheduled day. An additional window for testing procedure due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons) is specified in the SOE. For image tests (CT scan, positron emission tomography [PET] with ^{18}fluorodeoxyglucose [FDG-PET], MUGA scan, echocardiography), a ±7-day window is allowed.

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

9.4.1 Informed Consent

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

9.4.2 Patient Demographics

The date of birth, 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 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 and the best response achieved by each one. In addition, concomitant medications will be recorded as specified in Section 9.4.10.

Available tumor genomic information obtained at the site will be collected.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A). Any clinically relevant findings are to be documented.

9.4.5 Patient Height and Weight

Height will be measured only during screening. Body weight should be recorded as specified in the SOE (Appendix A).

9.4.6 ECOG Performance Status

Performance status is to be assessed using the ECOG scale (see Appendix D for a description of the scale) at the times specified in the SOE (Appendix A).

9.4.7 Vital Signs

Vital signs (blood pressure, heart rate, and temperature) will be monitored as specified in the SOE (Appendix A).

9.4.8 Viral Serologies

Serological tests for hepatitis B (hepatitis B surface antigen [HBsAg] and IgG anti-hepatitis B core antibody), hepatitis C virus ([HCV]-antibody, also HCV-RNA by polymerase chain reaction if the patient is HCV-antibody positive), and HIV at screening period. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-hepatitis B core antibody [anti-HBc] positive), consult with physicians with expertise in managing hepatitis B regarding monitoring.

9.4.9 Pregnancy Test

A serum/urine pregnancy test will be obtained for women of childbearing potential at screening, C1D1, on Day 1 of each cycle, and at the EOT. The screening results must be available and negative before enrollment. For women of childbearing potential, if menstrual period is delayed during the study, absence of pregnancy must be confirmed by serum pregnancy test.

Pregnancy tests may also be repeated during the study if requested by an IRB or if required by local regulations.

9.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.7 for a list of medications and therapies that are prohibited during the study.

9.4.11 AEs

Monitoring of AEs, serious and nonserious, will be conducted from the time of informed consent throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.12 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug.

Procedures for completing enrollment information are described in the study manual.

9.4.13 Cardiac Monitoring

9.4.13.1 12-Lead ECGs and LVEF

A single 12-lead standard safety ECG will be performed to assess eligibility as specified in the SOE (Appendix A). ECG assessments are to be performed with the patient supine and rested for at least 5 minutes before collection. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

The assessment of LVEF measured by echocardiography or MUGA scan will be performed as indicated in SOE. From Cycle 2 onwards, a ±7 day window is allowed for this test. When the timing of ECG or vital sign measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first followed by blood sampling.

9.4.13.2 [redacted]

[redacted]

9.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Additional handling and shipment of clinical laboratory samples will be outlined in the study manual.

9.4.14.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematology 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 SOE (Appendix A). They will be performed locally only. Predose samples may be collected up to 3 days before the visit.

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	Activated partial thromboplastin time
Hemoglobin	Alkaline phosphatase	Prothrombin time
Leukocytes with differential [a]	Alanine aminotransferase	Fibrinogen
ANC	Aspartate aminotransferase	
CD4/CD8 count and ratio	Bilirubin (total)	
Platelet count	(Blood) Urea nitrogen	
	Calcium	
	Bicarbonate or Carbon dioxide	
	Creatinine	
	(Standard) C Reactive protein	
	Chloride	
	Glucose	
	Lactate dehydrogenase	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Protein (total)	
	Urate	

ANC: absolute neutrophil count.
[a] Differential laboratory results may be entered in unit types of "Absolute," "Percent," "Both," or "Not applicable." "Absolute" values are preferred when available.

The chemistry laboratory parameters for TLS monitoring will include the following: creatinine, uric acid, potassium, phosphorus, calcium, albumin, and corrected calcium, if available.

Table 9.b Clinical Urinalysis Tests

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

Hematology, chemistry, coagulation and urine samples may be taken up to 3 days before the visit (unless otherwise specified). All results must be evaluated before dosing. Microscopic analysis of urine sediment should be performed if significant abnormalities are detected in proteins, leukocytes, or blood.

Serum creatinine clearance is to be estimated by the Cockcroft-Gault formula (Cockcroft and Gault 1976) as follows:

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

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

9.4.14.2 Immunosafety Markers

Blood samples for the analysis of autoimmune endocrinopathies as shown in Table 9.c will be obtained as specified in the SOE (Appendix A). They will be performed locally only. Results may be evaluated after dosing.

Table 9.c Immunosafety Determinations in Serum

Serum Chemistry	
Thyrotropin	Free thyroxine
	Adrenocorticotropic hormone

9.4.14.3 Complement System Proteins

Blood samples for the analysis and quantification of the complement proteins C1q, C3, C4, and CH50 will be obtained as specified in the SOE (Appendix A). They will be performed locally only. Results may be evaluated after dosing.

9.4.15 Disease Assessment

9.4.15.1 Imaging

Appropriate cancer staging assessments should be performed (eg, MRI, FDG-PET-CT). Imaging assessments should be conducted according to Lugano Classification for staging and response assessment (Cheson et al. 2014). A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis in addition to an FDG-PET scan must be acquired at screening. Subsequently, the same imaging modality used at screening should be used throughout the study whenever possible. It is understood that some circumstances may require a different imaging modality. An alternate imaging modality is acceptable and may be performed at the investigator's discretion. Objective assessments of the disease burden: target, non-target, and potential new lesions will be performed at each time point (a ±7-day window is allowed for image tests) as described in the SOEs (Appendix A). Radiographic images will be maintained at the site and can be requested by the sponsor at a later date. For Phase 2, radiographic images must be submitted to a centralized repository for future centralized review should that be required or desired. Imaging tests performed before the screening consent date may be used, if of diagnostic quality, as screening tests if the C1D1 is planned within the 28 days after the date of the test.

9.4.15.2 Bone Marrow Biopsy and Aspirate

During Phase 2 only, 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 disease progression 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 clinical study report will be based on investigator assessment.

9.4.16 [redacted], Pharmacodynamic, and PK Samples

9.4.16.1 Tumor Biopsies (Global Study; Not Applicable to Patients Enrolled in China)

Banked Tumor

Banked formalin-fixed, paraffin-embedded tumor tissue (preferred) or 10 unstained slides of the tumor tissue obtained ≤12 months prior to screening will be collected, if available, from all enrolled patients to assess baseline features: [redacted] See the laboratory manual for details.

Fresh Tumor Biopsy

Screening and on-treatment tumor biopsies are optional for patients enrolled during Phase 1. The optional on-treatment fresh tumor biopsies in Phase 1 will be collected on Cycle 2, Day 8 (+7 days). When possible, screening and on-treatment biopsies will be collected from the same lesion. Collection timing of the on-treatment biopsy may be changed, should data collected during the study be supportive of such a change. A decision to stop tumor biopsies collection may take place should sufficient tumor-related data be generated.

If a tumor biopsy procedures is performed it should be done according to standard site practice; further the lesion must be accessible for a low-risk biopsy procedure as assessed by the investigator. The tumor biopsy procedure will be performed by core needle or surgically, if the site of disease is superficial and palpable or visible. [redacted]

[redacted]

9.4.16.2 Skin Biopsies Measurements (Phase 1 only)

Patients must be willing to consent to 1 mandatory pretreatment and 1 on-treatment skin biopsy during Phase 1. The skin biopsy entry requirement may be discontinued by the sponsor once there is enough pharmacodynamic evidence of target engagement.

All skin punch biopsies should be obtained from the upper back following institutional guidelines from all patients at prespecified time points, as outlined in the SOE (Appendix A), to detect the formation of SUMO-TAK-981 adducts and inhibition of SUMO2/SUMO3. A decision to stop skin punch biopsies collection may take place should sufficient data related to target engagement and SUMO2/SUMO3 inhibition be generated.

9.4.17 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Laboratory Manual. Plasma samples for PK will be collected at the time points specified in Appendix A, Table A-3, and Table A-4. Plasma samples should be collected from the contralateral arm (not the arm which was used for drug infusion).

The timing, but not the total number of plasma samples for PK and/or ECG samples, may be modified during the study based on emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK and PK-QTc interval relationship of TAK-981. A protocol amendment is not necessary for such modifications.

Plasma collected in this study will be used to measure the level of TAK-981 including the exploration of TAK-981 related metabolites to understand TAK-981 metabolism and excretion mechanisms. The results of such exploratory metabolite analyses (qualitative or semi-quantitative) will be presented in a separate report and not in the clinical study report for this study.

9.4.18 Pharmacodynamic Measurements

The pharmacodynamics specimen collection time points are displayed in Appendix A, Table A-5, Table A-6, and Table A-7 (for China Biomarkers). Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

Collection of samples for exploratory endpoints are dependent upon local guidelines and regulations (including feasibility of sample export), as well as IRB/IEC approval.

The following pharmacodynamic measures will be tested in the global study (excluding patients enrolled in China):

- TAK-981–SUMO adduct formation and SUMO2/SUMO3 inhibition in skin biopsy and blood (Phase 1).

[redacted]

[redacted]

[redacted]

The following are China-specific pharmacodynamic measurements (Table A-7):

[redacted]

9.4.19 [redacted]

[redacted]

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment when they have discontinued treatment with TAK-981.

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are discontinued from study drug and 1 or more of the following situations occur:

- Death.
- PD
- Start of new systemic treatment.
- Withdrawal by patient.
- Study terminated by the sponsor.
- Lost to follow-up.
- Transfer of patient to a TAK-981 long-term safety study, single-patient investigational new drug application, or similar program.

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

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Patients will be informed that they have the right to discontinue study treatment at any time for any reason, without prejudice to their medical care.

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

- Pregnancy.
- Withdrawal by patient.
- AE that leads to TAK-981 discontinuation.
- Death.
- Initiation of another systemic anticancer treatment.
- Study terminated by sponsor.
- Treatment completion, ie, the patient completes 1 year of treatment and continuation is not approved.

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

- Symptomatic deterioration.
- Clinical progression.
- PD.
- CR (after discussion with sponsor).
- Major protocol deviation.
- Lost to follow-up.
- Lack of benefit.

Once TAK-981 has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course (Section 9.9); these patients will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) until death occurs.

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

In the case of study termination by the sponsor, eligible patients may have continued access to TAK-981 as described in Section 6.5.5.

9.8 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.

9.9 Posttreatment Follow-up Assessments

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks ±1 week from the last dose of study drug until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, or study termination (Section 9.6), whichever occurs first. The duration of follow-up for PFS will be up to a maximum of 12 months for each patient, or until 50% of patients have progressed, whichever occurs first.

During Phase 2, patients who stop treatment due to PD will be followed every 12 weeks (±1 week) after documented PD for OS until death, loss to follow-up, consent withdrawal, or study termination for up to 12 months after the last patient discontinues or completes treatment, or until 50% of patients have died, whichever occurs first. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

Subsequent follow-up for PFS and OS, respectively, will be calculated from last contact.

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

9.10 Early Study Termination

The study may be terminated early by the sponsor at any time for reasons that may include a potential health hazard to patients, poor enrollment of patients (thus, making completion of the trial in an acceptable timeframe unlikely), or modification or discontinuation of study drug development.

The study may be stopped or terminated in a country if the favorable opinion or the approval in that country is revoked by that country's ethics committee as mandated by German law.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

All abnormal laboratory values will be reviewed by the investigator but only those abnormal values that lead to discontinuation or delay in treatment, dose modification, therapeutic intervention, or are considered by the investigator to be a clinically significant change from baseline will be assessed as AEs.

Disease progression of the malignancy under study assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE. However, worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the eCRF.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Any death, whether due to side effects of the treatment, PD, or other causes is considered an SAE.

Hospitalization for previously planned procedure(s) or convenience will not be considered as a reportable SAE.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

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

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

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 5.0; except CRS which will be graded according to ASTCT Consensus Grading for CRS (Lee et al. 2019). The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), the start of second line alternative therapy, or 6 months after PD has occurred, whichever comes first.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 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).

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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. 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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. If transmission of a pregnancy report is not feasible, then a facsimile of the completed Takeda paper-based pregnancy form will be sent.

Pregnancies are to be reported through 12 months after the last dose of study drug.

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

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

A medication error is a preventable event that involves an identifiable patient and 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 email address provided below.

Product	Call Center	Email
TAK-981	Takeda	ctmcomplaint@takeda.com

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

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 and any other applicable SAEs to regulatory authorities, including investigators and IRBs, as applicable, in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 SMC

During Phase 1, an SMC composed of the principal investigators and sponsor clinician will regularly review safety data to ensure patient safety throughout the study and make decisions on dose escalation as defined in the SMC charter.

11.2 IDMC

During Phase 2, an IDMC will be established to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study. The IDMC will consist of 3 to 5 members not associated with the conduct of the study and/or the sponsor with the exception of the compensation to IDMC members related to their IDMC activities. The IDMC members will be a multidisciplinary group that will include at least 2 hematologists with extensive experience in clinical study conduct and a biostatistician with substantial experience in the IDMC process. The committee will perform data review to monitor safety and assess benefit/risk throughout the conduct of the Phase 2 portion of the study. IDMC meetings will be held at the end of each stage for each of the respective arms in Phase 2. Ad-hoc IDMC meetings may also be held if a significant issue should arise.

11.3 Independent Review Committee

All imaging performed to assess response to treatment will be submitted to a central core imaging repository. An independent review committee (IRC) will be established to independently review efficacy imaging endpoints once any cohort in Phase 2 meets the efficacy threshold in Stage 1 and begins enrolling patients in Stage 2. Please refer to the imaging manual and/or IRC charter for further details.

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, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

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

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

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

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the 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 designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study-site agreement between the investigator and sponsor.

Refer to the clinical study-site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan 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.

13.1.1 Analysis Sets

The analysis sets will include the following:

Safety analysis set: Patients who have received at least 1 dose, even if incomplete, 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.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients enrolled in the Phase 1 portion of the study who experienced a DLT at any time after initiation of the first infusion of TAK-981 or who completed all planned infusions of TAK-981 and 3 infusions of rituximab without experiencing a DLT. The DLT-evaluable population will be used to determine the RP2D/MTD.

Response-evaluable analysis set: Patients who have received at least 1 dose of study drug, have sites of measurable disease at baseline, and 1 postbaseline disease assessment, or were discontinued due to symptomatic deterioration or death before postbaseline evaluation happened, will be used for analyses of response.

Pharmacodynamic analysis sets:

Pharmacodynamic analysis sets to assess target engagement of TAK-981 and SUMOylation pathway inhibition:

- Patients who have provided evaluable skin biopsies (screening sample and postdose sample) will be included in the *skin pharmacodynamic analysis dataset*.
- Patients who have provided evaluable blood samples (C1D1 predose sample and at least 1 postdose sample) will be included in the *blood pharmacodynamic analysis dataset*.

[redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include gender, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts, and percentages will be provided. Categories for missing data will be presented as needed.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

Phase 1:

Efficacy is not the primary objective for this study in the Phase 1 portion. The efficacy analysis will mainly focus on the Phase 2 portion of this study.

In the Phase 1 portion of this study, efficacy parameters such as ORR, DOR, and PFS may be summarized as appropriate. Disease response will be categorized and presented in listings.

Phase 2:

The primary endpoint for Phase 2 portion is ORR (CR + PR) as defined by the investigator according to Lugano criteria for lymphoma response, from Cheson 2014 (Cheson et al. 2014).

ORR is defined as the proportion of patients who achieve CR and PR (determined by the investigator) during the study.

The primary efficacy analysis will be based on the response-evaluable population in the Phase 2 portion of the study.

Estimates of the ORR (CR + PR) will be presented with 2-sided 95% exact binomial confidence intervals.

13.1.3.2 Secondary Efficacy Analysis

Secondary efficacy endpoints include DCR, DOR, TTP, and PFS.

DCR is defined as the proportion of patients who achieve CR, PR, or SD (determined by the investigator) during the study.

DOR is the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders (PR or better). Responders without documentation of PD will be censored at the date of last response assessment that is stable disease or better.

TTP is defined as the time from the date of first study drug administration to the date of first documented disease progression by the investigator.

PFS is defined as the time from the date of the first dose administration to the date of first documentation of PD or death due to any cause, whichever occurs first. PD will be determined by

Response Evaluation Criteria in Lymphoma for patients with lymphoma. Patients without documentation of PD will be censored at the date of the last response assessment that is stable disease or better.

PFS will be analyzed descriptively using Kaplan-Meier method for safety analysis set. DOR will be analyzed using Kaplan-Meier method for response-evaluable analysis set.

13.1.4 PK Analysis

The PK of TAK-981 will be characterized in this study (ie, rituximab PK will not be characterized).

PK parameters for TAK-981 will be estimated using noncompartmental methods with Phoenix WinNonlin software. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be estimated, as permitted by data, for samples collected during C1D1 and C1D8:

- C_{max}.
- t_{max}.
- $AUC_{0-\infty}$.
- AUC_{0-t}.
- $t_{1/2z}$.
- CL.
- V_{ss}.

PK parameters will be summarized using descriptive statistics. Individual TAK-981 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort. The above parameters will not be estimated for the sparse PK samples collected during the Phase 2 portion of study.

The serial and sparse PK data collected in this study are intended to contribute to future population PK analyses of TAK-981. These population PK analyses may include data collected in other TAK-981 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

13.1.5 Pharmacodynamic Analysis

The analysis of blood and skin biomarker profiles for each dose and timepoint tested will be tabulated. When possible, the dynamic range for each biomarker and fold change will be determined to better understand TAK-981 biological activity range and duration of pharmacodynamic effect, and to help determine the PAD/RP2D for the TAK-981/rituximab combination. [redacted]

13.1.6 PK/Pharmacodynamic Analysis

Data permitting, the PK and pharmacodynamic data collected in this study will be analyzed to understand the exposure-response relationship for TAK-981 in combination with rituximab. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 in combination with rituximab and for determination of PAD.

To determine the appropriateness of the PAD/MTD and schedule, a totality of evidence approach will be used that will integrate all available data from the dose escalation and the Phase 2 portions of the study including:

1. Multicycle safety/tolerability of TAK-981 in combination with rituximab.
2. Single and multiple dose PK of TAK-981.
3. Single and multiple dose pharmacodynamic biomarkers of TAK-981 (in circulation and skin), including target engagement (adduct formation) and SUMO2/SUMO3 inhibition [redacted]
4. Antitumor response with TAK-981 in combination with rituximab administration.
5. Relative dose intensity.

Dose-exposure-response relationships will be explored to describe the PK-safety, PK-pharmacodynamics, and PK-antitumor response relationships of TAK-981, and the results of such quantitative pharmacology analyses will be used to inform selection of the RP2D/schedule of TAK-981 in combination with rituximab.

In addition, the PK-pharmacodynamic data collected in the study during dose escalation may be used to inform the quantitative systems pharmacology model that may be used to further refine the dose/schedule for TAK-981. Furthermore, the PK-pharmacodynamic data collected in this study may be pooled with similar data from other clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and quantitative systems pharmacology modeling may not be presented in the clinical study report for this study but will be presented in a separate report.

13.1.7 [redacted]

[redacted]

13.1.8 Safety Analysis

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 analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients).
- SAEs (related and regardless of relationship).
- TEAE leading to study drug modification and discontinuation.

The incidence of DLTs will be tabulated using the DLT-evaluable analysis set.

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

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG Performance Scores will be summarized using a shift table.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the TAK-981 safety profile.

All concomitant medications collected from the first dose of study drug throughout the study period will be classified to preferred terms according to the World Health Organization drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-981.

13.2 Interim Analysis and Criteria for Early Termination

In Phase 1, investigators and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort in the dose-escalation phase (see Section 8.5).

During the Phase 2 part of the study, interim analysis for futility will be performed for each of the cohorts upon completion of the respective Stage 1.

13.3 Determination of Sample Size

It is anticipated that up to approximately 180 patients will be enrolled in this study, including the dose-escalation phase (approximately up to 35 patients), and the 5 expansion dose cohorts (A 120 mg, B 120 mg, B 60 mg, C 120 mg, and C 60 mg) for Phase 2 (up to approximately 145 response-evaluable patients) to evaluate efficacy in patients with select lymphoma.

Dose-Escalation Phase (Phase 1):

It is estimated that up to approximately 35 DLT-evaluable patients will be enrolled in this study for the dose-escalation phase.

An adaptive BLRM that implements escalation with overdose control will be used to for purposes of dose-escalation recommendations and estimation of the MTD and/or PAD. We assume a group of approximately 3 patients will be enrolled in a combination dose cohort-based on an adaptive design using BLRM with safety data evaluation and PK guidance. The actual cohort size during the study is flexible and may be different from 3 patients. The total number of patients in the dose escalation is dependent on the observed safety profile and PK/pharmacodynamics guidance, which will determine the number of patients per combination dose cohort, as well as the number of dose escalations required to achieve MTD and/or PAD. The selection of the next recommended dose will be determined from BLRM along with consideration of other safety, clinical, PK, and pharmacodynamic data, including data from the FIH study (TAK-981-1002).

The description, prior calibration, and operating characteristics of the BLRM are included in Appendix H.

Efficacy-Evaluation Phase (Phase 2):

After MTD/PAD is defined, up to approximately 145 response-evaluable patients with 2 specified types of lymphomas will be enrolled in parallel in a Phase 2 study to evaluate the efficacy of TAK-981.

The primary endpoint for the Phase 2 portion is ORR (CR + PR) as assessed by the investigator according to Lugano criteria for patients with lymphoma. The sample size consideration for disease-specific patient populations is adaptive design based on Simon's 2-stage design for a single proportion (Lin and Shih 2004) with the following hypotheses of ORR.

[redacted]

[redacted]

Table 13.a [redacted]

[redacted]

[redacted]

Table 13.b [redacted]

[redacted]

Table 13.c [redacted]

[redacted]

Patients enrolled at the Phase 2 dose levels in the Phase 1 portion of this study may be pooled with patients in the Phase 2 portion of this study for safety evaluations. However, only patients enrolled in a Phase 2 cohort will be considered for statistical efficacy analyses of Phase 2 responses.

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. If monitors are not allowed to visit sites for data verification due to pandemic (eg, COVID-19), remote electronic medical records access visits may be conducted (where allowed by sites). 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 and by the IRB or IEC.

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or

misconduct, increase the health risk to the subject, or confound interpretation of the primary study assessment.

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator 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 Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the United States 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, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be

obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify sites once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the study. Until the site receives drug, no protocol activities, including screening, may occur.

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

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

15.2 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, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed

consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

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

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

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

15.3 Patient Confidentiality

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

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

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

15.4.2 Clinical Trial Registration

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

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Events

SOEs for patients enrolled in the global study (except for those enrolled in China) are:

- Phase 1: Table A-1, Table A-3 (PK assessments), and Table A-5 (biomarker sample collection).
- Phase 2: Table A-2, Table A-4 (PK assessments), and Table A-6 (biomarker sample collection).

SOEs for patients enrolled in China (Phase 2 only) are:

- Table A-2, Table A-4 (PK assessments), and Table A-7 (biomarker sample collection).

Table A-1 SOE for Phase 1 (Global Patients Only; Excluding Patients Enrolled in China)

Procedure/Assessment	Screening [a]	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 9	Cycle 1 Day 11	Cycle 1 Day 15	Cycle 2 and Subsequent Cycles Day 1	Cycle 2 and Subsequent Cycles Day 4	Cycle 2 and Subsequent Cycles Day 8	Cycle 2 and Subsequent Cycles Day 11	Cycle 2 and Subsequent Cycles Day 15	EOT 30 (+10) d after Last TAK-981 Dose	Follow-up [b] Every 12 Wks PFS	Follow-up [b] Every 12 Wks OS
Informed consent	X															
Inclusion/exclusion criteria	X															
Demographics	X															
Medical history including available tumor information [c]	X															
Physical examination [d]	X															
Symptom-directed physical examination									X					X		
Height	X															
Weight [d]	X								X					X		
ECOG performance status	X	X							X					X		
Vital signs [e]	X	X		X [f]	X		X [f]	X [f]	X	X [f]	X	X [f]	X [f]	X		
12-lead safety ECG (single record) [g]	X	X2			X2				X2					X		
[redacted]																
Echocardiography/MUGA (LVEF) scan [i]	X								X [j]					X		
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug.													X		
AE reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug or start of a new systemic treatment.													X		
	SAEs will be reported from signing of the ICF through 30 days after the last dose of study drug or any moment after EOT for related SAEs [g]													X		
Treatment Administration																
TAK-981 administration [k]		X		X [f]	X		X [f]	X [f]	X	X [f]	X	X [f]	X [f]			
Rituximab administration [k]		X			X			X	X							

Procedure/Assessment	Screening [a]	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 9	Cycle 1 Day 11	Cycle 1 Day 15	Cycle 2 and Subsequent Cycles Day 1	Cycle 2 and Subsequent Cycles Day 4	Cycle 2 and Subsequent Cycles Day 8	Cycle 2 and Subsequent Cycles Day 11	Cycle 2 and Subsequent Cycles Day 15	EOT 30 (+10) d after Last TAK-981 Dose	Follow-up [b] Every 12 Wks PFS	Follow-up [b] Every 12 Wks OS
Samples/Laboratory Assessments																
Viral serologies [l]	X															
Pregnancy test [m]	X	X							X					X		
Hematology/Chemistry [n]	X	X			X			X	X		X [j]			X		
TLS laboratory assessments [o]		X	X													
Coagulation [n]	X								X					X		
Urinalysis [n, p]	X				X				X					X		
Immunosafety markers (hormones) [q]	X								X					X		
Complement serum proteins [n]	X				X			X	X					X		
Disease Assessment/Survival Follow-up																
Imaging [r]	X	Every 2 months from C1D1 for the first 6 months, and every 12 weeks thereafter.												X	X	
Bone marrow biopsy [s]		X Refer to Section 9.4.15.2 for details.												X	X	
Investigator assessment of disease response		Every 2 months from C1D1 for the first 6 months, and every 12 weeks thereafter.												X	X	
Survival follow-up																X
Subsequent therapy																X
Central Laboratory Sample Collection																
PK sample collection	Refer to Phase 1 Table A-3.															
Biomarker sample collection	Refer to Phase 1 Table A-5.															

AE: adverse event; anti-HBc: anti-hepatitis B core antibody; COVID-19: coronavirus disease 2019; C1D1: Cycle 1 Day 1; C1D8: Cycle 1 Day 8; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; FDG-PET: ^{18}fluorodeoxyglucose positron emission tomography; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HCV-Ab: hepatitis C virus antibody; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; LVEF: left ventricular ejection fraction; mos: months; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic; SAE: serious adverse event; SOE: schedule of events; TLS: tumor lysis syndrome; X2: two timepoints.

Tests and procedures should be performed on schedule (unless otherwise specified in Section 9.0); occasional changes are allowable up to a 4-day window for inclement weather, holidays, vacations, and other administrative reasons. From Cycle 2 onwards, laboratory assessments may occur up to 3 days before the scheduled day. Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. For individual instances where assessments or procedures are not able to be performed as defined in the protocol, the reasons for failing to perform those should be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified visit, assessment, or procedure). If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor. If a visit or procedure cannot be performed within the window, then the Takeda project clinician or designee should be consulted if a longer window is necessary. If the study schedule, especially including dosing, is shifted, assessments should be shifted to align with the new schedule. A cycle of therapy begins when a patient receives a dose of TAK-981 or of rituximab.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Signed informed consent must be obtained before performing any protocol-specific procedure. Informed consent must be documented before initiating any screening procedures that are for research purposes only. Tests and the resultant findings, which are done before consent for standard of care reasons, may count towards a screening procedure if done within 28 days of the first dose of TAK-981.

[b] Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from last dose of study drug until PD. Response to treatment will also continue to be assessed in PFS follow-up every 12 weeks for patients who discontinue treatment for reasons other than PD until occurrence of PD, start of alternative therapy, or conclusion of the study. After the occurrence of PD or start of alternative therapy, patients will continue to have OS follow-up visits that may be performed by phone contact. The OS information will be collected every 12 weeks after the last dose of study drug until death or the conclusion of the study, whichever occurs first.

[c] Available pathology/cytogenetic/mutational information for all patients should be reported in the eCRF.

[d] Complete physical examination at screening. If the assessment was performed more than 3 days before C1D1, the examination should be performed again. Weight should be recorded during screening.

[e] Perform vital signs measurements before and after dosing. Blood pressure, heart rate, and temperature will be measured immediately before the start of the infusion and at the end of the infusion of each study drug. Blood pressure should be determined with the patient in a supine position after the patient has been quiet for 5 minutes. Outside C1D1, all patients will be monitored for 2 hours after the end of infusion of the last study drug. After the administration of TAK-981 or rituximab, the patient should be considered clinically stable by the investigator or designee before the next study drug is administered or the patient is discharged. If no infusion reaction is observed in the first 2 cycles, post-infusion monitoring may not be required and the patient can be discharged from the site per investigator discretion.

[f] During Phase 1 of this study, if alternative dosing schedules for TAK-981 (eg, TAK-981 on Day 1, or Days 1, 4, 8 and 11, or Days 1, 8, and 15 every 21 days) were employed, this test, dose administration, or procedure were performed on dosing days. For patients enrolled in a less dense schedule (eg, TAK-981 on Day 1 every 21 days), this test, procedure, or dosing was not performed.

[g] Predose and post-EOI (+1 h window) 12-lead ECG will be collected on C1D1, C1D8, and on Day 1 of every other subsequent cycle (Cycles 2, 4, 6, 8, etc). Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed after the patient has rested for 5 minutes.

[h] [redacted]

[i] The MUGA (LVEF) scan should be performed at the screening to ensure patient eligibility. Echocardiographic estimate of the LVEF can be measured as an alternative to MUGA scans.

[j] Cycle 2 only.

[k] On C1D1 only, rituximab will be administered first (before TAK-981 infusion). At least 1 hour should elapse between the completion of the infusion of the first study drug and the initiation of the infusion of the second study drug. For the first infusion (C1D1) of TAK-981 in combination with rituximab during dose escalation in Phase 1, every patient must be observed for 4 hours after the EOI. From C1D8 onwards, TAK-981 will be administered before rituximab on the days on which both agents are administered on the same day visit and the patient can be discharged from observation after a minimum of 2 hours after the end of infusion only if there are no signs and symptoms of acute toxicity like fever, significant changes in blood pressure and/or heart rate. Dose administration should be performed on schedule; however, a dose delay of up to 4 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor. If a treatment visit is delayed, associated tests and procedures should also be delayed. At least 7 days should elapse between consecutive doses of rituximab. For further details on TAK-981 or rituximab administration refer to Section 8.1.

[l] HBsAg, IgG anti-HBc, HCV-Ab serology (also HCV-RNA by polymerase chain reaction if the patient is HCV-antibody positive), and HIV-Ab. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring.

[m] A serum/urine choriogonadotropin beta (β-hCG) pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 3 days before the first dose of any study drug. The results must be negative within 3 days before the first dose of TAK-981/rituximab is administered (ie, within the 3 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, if the menstrual period is delayed, upon request of an IEC/IRB, or if required by local regulations.

[n] Hematology, CD4/CD8-T-cells count and ratio, chemistry, coagulation, complement serum protein, and urine samples may be taken up to 3 days before the visit.

[o] For patients hospitalized due to high TLS risk, monitor blood chemistries at 4, 8, 12, and 24 hours and, as needed, after rituximab dose (Sections 8.10.8 and 9.4.14).

[p] Urinalysis includes tests for pH, proteins, glucose, ketone bodies, urobilinogen, bilirubin, leukocytes, erythrocytes, nitrites, density, and sediment. From Cycle 2 onwards, urine tests will be taken only the first day of each cycle and at EOT.

[q] Immunosafety determinations include thyroid-stimulating hormone, free thyroxine, and adrenocorticotropic hormone measured in blood and repeated at the beginning of each cycle until Cycle 6, every other cycle afterwards, and at the end of study treatment.

[r] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis in addition to an FDG-PET scan must be acquired at screening. Subsequently, the same imaging modality (contrast-enhanced CT or MRI, and FDG-PET scan) should be performed. Imaging tests performed before the screening consent date may be used as screening tests if the C1D1 is planned within the 28 days after the date of the test. Refer to Section 9.4.15.1 for details.

[s] In Phase 1, bone marrow biopsy will be performed at screening per investigator discretion and Lugano guidelines to assess bone marrow involvement.

Table A-2 SOE for Phase 2 (All Patients, Including Patients Enrolled in China)

Procedure/Assessment	Screening [a]	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 9	Cycle 1 Day 11	Cycle 1 Day 15	Cycle 2 and Subsequent Cycles Day 1	Cycle 2 and Subsequent Cycles Day 4	Cycle 2 and Subsequent Cycles Day 8	Cycle 2 and Subsequent Cycles Day 11	Cycle 2 and Subsequent Cycles Day 15	EOT 30 (+10) d after Last TAK-981 Dose	Follow-up [b] Every 3 Mos PFS	Follow-up [b] Every 3 Mos OS
Informed consent	X															
Inclusion/exclusion criteria	X															
Demographics	X															
Medical history including available tumor information [c]	X															
Physical examination [d]	X															
Symptom-directed physical examination									X					X		
Height	X															
Weight [d]	X	X							X					X		
ECOG performance status	X	X							X					X		
Vital signs [e]	X	X			X			X [f]	X		X			X		
12-lead safety ECG (single record) [g]	X	X2			X2				X2		X2			X		
Echocardiography/MUGA (LVEF) scan [h]	X								X [i]					X		
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug.													X		
AE reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug or start of a new systemic treatment.													X		
	SAEs will be reported from signing of the ICF through 30 days after the last dose of study drug or any moment after EOT for related SAEs													X		
Treatment Administration																
TAK-981 administration [j]		X			X				X		X					
Rituximab administration [j]		X			X			X	X							
Samples/Laboratory Assessments																
Viral serologies [k]	X															

Procedure/Assessment	Screening [a]	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 9	Cycle 1 Day 11	Cycle 1 Day 15	Cycle 2 and Subsequent Cycles Day 1	Cycle 2 and Subsequent Cycles Day 4	Cycle 2 and Subsequent Cycles Day 8	Cycle 2 and Subsequent Cycles Day 11	Cycle 2 and Subsequent Cycles Day 15	EOT 30 (+10) d after Last TAK-981 Dose	Follow-up [b] Every 3 Mos PFS	Follow-up [b] Every 3 Mos OS
Pregnancy test β-HCG (urine or serum) [l]	X	X							X					X		
Hematology/Chemistry [m]	X	X			X			X	X		X [i]			X		
TLS laboratory assessments [n]		X	X													
Coagulation [m]	X								X					X		
Urinalysis [m, o]	X								X					X		
Immunosafety markers (hormones) [p]	X								X					X		
Complement serum proteins [m]	X				X			X	X					X		
Disease Assessment/Survival Follow-up																
Imaging [q]	X	Every 2 months from C1D1 for the first 6 months, and every 12 weeks thereafter.												X	X	
Disease Assessment	X	Every 2 months from C1D1 for the first 6 months, and every 12 weeks thereafter.												X[n]	X	
Bone marrow biopsy [r]	X	X Refer to Section 9.4.15.2 for details.												X	X	
Survival follow-up																X
Subsequent therapy																X
Central Laboratory Sample Collection																
PK sample collection	Refer to Phase 2 Table A-4.															
Biomarker sample collection	Refer to Phase 2 Table A-6 (global study) and Table A-7 (for patients enrolled in China)															

AE: adverse event; anti-HBc: anti-hepatitis B core antibody; COVID-19: coronavirus disease 2019; C1D1: Cycle 1 Day 1; C1D8: Cycle 1 Day 8; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOI: end of infusion; EOT: end of treatment; FDG-PET: ^{18}fluorodeoxyglucose positron emission tomography; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HCV-Ab: hepatitis C virus antibody; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; LVEF: left ventricular ejection fraction; mos: months; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic; q12w: every 12 weeks; SAE: serious adverse event; SOE: schedule of events; TLS: tumor lysis syndrome; X2: two timepoints.

Tests and procedures should be performed on schedule (unless otherwise specified in Section 9.0); occasional changes are allowable up to a 4-day window for inclement weather, holidays, vacations, and other administrative reasons. Laboratory assessments may occur up to 3 days before the scheduled day. Unless otherwise noted, evaluations during the treatment period must occur before drug administration on scheduled visits. For individual instances where assessments or procedures are not able to be performed as defined in the protocol, the reasons for failing to perform those should be documented (eg, identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified visit, assessment, or procedure). If extenuating circumstances prevent a patient from completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor. If a visit or procedure cannot be performed within the window, then the Takeda project clinician or designee should be consulted if a longer window is necessary. If the study schedule, especially including dosing, is shifted, assessments should be shifted to align with the new schedule. A cycle of therapy begins when a patient receives a dose of TAK-981 or of rituximab.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug (C1D1). Signed informed consent must be obtained before performing any protocol-specific procedure.

[b] Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from last dose of study drug until PD. Response to treatment will also continue to be assessed in PFS follow-up every 12 weeks for patients who discontinue treatment for reasons other than PD until occurrence of PD, start of alternative therapy, or conclusion of the study. After the occurrence of PD or start of alternative therapy, patients will continue to have OS follow-up visits that may be performed by phone contact. The OS information will be collected every 12 weeks after the last dose of study drug until death or the conclusion of the study, whichever occurs first.

[c] Available pathology/cytogenetic/mutational information for all patients should be reported in the eCRF.

[d] Complete physical examination at screening. If the assessment was performed more than 3 days before C1D1, the examination should be performed again. Weight should be recorded during screening.

[e] Perform vital signs measurements before and after dosing. Blood pressure, heart rate, and temperature will be measured immediately before the start of the infusion and at the end of the infusion of each study drug. Blood pressure should be determined with the patient in a supine position after the patient has been quiet for 5 minutes. Outside C1D1, all patients will be monitored for 2 hours after the end of infusion of the last study drug. After the administration of TAK-981 or rituximab, the patient should be considered clinically stable by the investigator or designee before the next study drug is administered or the patient is discharged. If no infusion reaction is observed in the first 2 cycles, post-infusion monitoring may not be required and the patient can be discharged from the site per investigator discretion.

[f] During Phase 1 of this study, if alternative dosing schedules for TAK-981 (eg, TAK-981 on Day 1, or Days 1, 4, 8 and 11, or Days 1, 8, and 15 every 21 days) were employed, this test, dose administration, or procedure were performed on dosing days. For patients enrolled in a less dense schedule (eg, TAK-981 on Day 1 every 21 days), this test, procedure, or dosing was not be performed.

[g] Predose and post-EOI (+1 h window) 12-lead ECG will be collected on C1D1, C1D8, and on Day 1 of every other subsequent cycle (Cycles 2, 4, 6, 8, etc). Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed after the patient has rested for 5 minutes.

[h] The MUGA (LVEF) scan should be performed at the screening to ensure patient eligibility. Echocardiographic estimate of the LVEF can be measured as an alternative to MUGA scans.

[i] Cycle 2 only.

[j] On C1D1 only, rituximab will be administered first (before TAK-981 infusion). At least 1 hour should elapse between the completion of the infusion of the first study drug and the initiation of the infusion of the second study drug. For the first infusion (C1D1) of TAK-981 in combination with rituximab, every patient must be observed for 4 hours after the EOI. From C1D8 onwards, TAK-981 will be administered before rituximab on the days on which both agents are administered on the same day visit and the patient can be discharged from observation after a minimum of 2 hours after the end of infusion only if there are no signs and symptoms of acute toxicity like fever, significant changes in blood pressure and/or heart rate. Dose administration should be performed on schedule; however, a dose delay of up to 4 days may occur because of inclement weather, holidays, vacations, or administrative reasons; a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor. If a treatment visit is delayed, associated tests and procedures should also be delayed. At least 7 days should elapse between consecutive doses of rituximab. For further details on TAK-981 or rituximab administration refer to Section 8.1.

[k] HBsAg, IgG anti-HBc, HCV-Ab serology (also HCV-RNA by polymerase chain reaction if the patient is HCV-antibody positive), and HIV-Ab. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring.

[l] A serum/urine choriogonadotropin beta (β-hCG) pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 3 days before the first dose of any study drug. The results must be negative within 3 days before the first dose of TAK-981/rituximab is administered (ie, within the 3 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, if the menstrual period is delayed, upon request of an IEC/IRB, or if required by local regulations.

[m] Hematology, CD4/CD8-T-cells count and ratio, chemistry, coagulation, complement serum protein, and urine samples may be taken up to 3 days before the visit.

[n] For patients hospitalized due to high TLS risk, monitor blood chemistries at 4, 8, 12, and 24 hours and, as needed, after rituximab dose (see Sections 8.10.8 and 9.4.14 for non-high risk patients).

[o] Urinalysis includes tests for pH, proteins, glucose, ketone bodies, urobilinogen, bilirubin, leukocytes, erythrocytes, nitrites, density, and sediment. From Cycle 2 onwards, urine tests will be taken only the first day of each cycle and at EOT.

[p] Immunosafety determinations include thyroid-stimulating hormone, free thyroxine, and adrenocorticotropic hormone measured in blood and repeated at the beginning of each cycle until Cycle 6, every other cycle afterwards, and at the end of study treatment.

[q] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis in addition to an FDG-PET scan must be acquired at screening. Subsequently, the same imaging modality (contrast-enhanced CT or MRI, and FDG-PET scan) should be performed. Informed consent must be documented before initiating any screening procedures that are for research purposes only. Tests, including imaging, and the resultant findings, which are done before consent for standard of care reasons may count towards a screening procedure if done within 28 days of the first dose of TAK-981. Refer to Section 9.4.15.1 for details.

[r] A bone marrow biopsy will be performed at screening during Phase 2 to assess bone marrow involvement only in patients with baseline PET-CT indicating negative bone marrow involvement. and to confirm complete response in all patients that are assessed as having a complete response. Refer to Section 9.4.15.2 for details.

Table A-3 Serial Plasma PK Sampling Schedule to Characterize PK of TAK-981 When Administered in Combination With Rituximab During Dose Escalation Phase 1 Only (Global Patients Only; Excluding Patients Enrolled in China)

	Cycle 1			Cycle 2	
	Day 1		Day 8	Day 1	Day 8
	[redacted]	PK (Plasma) [b]	PK (Plasma)	PK (Plasma)	PK (Plasma)
Predose (within 1 h before the start of TAK-981 infusion)		X1	X1	X1	X1
End of TAK-981 infusion (±10 min)		X1	X1	X1	X1
0.5 h after end of TAK-981 infusion (±10 min)		X1	X1		
1 h after end of TAK-981 infusion (±20 min)		X1	X1		
2 h after end of TAK-981 infusion (±30 min)		X1	X1		
4 h after end of TAK-981 infusion (±30 min)		X1	X1		
8 h after end of TAK-981 infusion (±30 min)		X1	X1		
24 h after end of TAK-981 infusion (±1 h)		X1	X1		
Total time points/samples		8	8	2	2

C1D1: Cycle 1, Day 1; C1D8: Cycle 1, Day 8; ECG: electrocardiogram; h: hour; min: minute(s); PK: pharmacokinetic; X1: 1 sample; X3: 3 measurements.

The date/time of the start and end of infusions should be recorded accurately. PK samples should only be collected from the contralateral arm and not from the drug infusion arm.

[a] [redacted]

[b] Only on C1D1, TAK-981 will be infused 1 hour after completion of the 4 hour rituximab infusion. All PK sampling time points in this table are in relation to TAK-981 infusion times and PK samples collected in this study will only be used to measure the PK of TAK-981 and exploration of TAK-981 related metabolites if needed (rituximab levels will not be measured). Starting from C1D8 onwards, TAK-981 will be administered as a 1-hour infusion to be completed before the start of 4-hour rituximab infusion. The timing of the morning visits should occur at approximately the same time as previous dosing days.

Table A-4 Sparse Plasma PK Sampling Schedule to Characterize PK of TAK-981 When Administered in Combination With Rituximab During Phase 2 Only (All Patients, Including Patients Enrolled in China)

	Cycle 1		Cycle 2	
	Day 1	Day 8	Day 1	Day 8
	PK (Plasma) [a]	PK (Plasma)	PK (Plasma)	PK (Plasma)
Pre–TAK-981 dose (within 1 h before the start of TAK-981 infusion)	X1	X1	X1	X1
End of TAK-981 infusion (±10 min)	X1	X1	X1	X1
1-4 hours after end of TAK-981 infusion (±30 min)	X1	X1		
Total time points/samples	3	3	2	2

CxDx: Cycle x, Day x; h: hour; min: minute(s); PK: pharmacokinetic; X1: 1 sample.

Rituximab infusion to be administered before TAK-981 infusion on C1D1 only, and after TAK-981 on all subsequent dosing days when both are administered.

[a] The timing of the morning visits should occur at approximately the same time as previous dosing days.

Table A-5 [redacted]

[redacted]

Table A-6 [redacted]

[redacted]

Table A-7 [redacted]

[redacted]

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the 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 a Form FDA 1572:

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

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

Appendix C Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix D 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, 1982 (Oken et al. 1982).
ECOG: Eastern Cooperative Oncology Group.

Appendix E Drugs That Interact With the CYP3A Family of CYPs

Drugs listed below that are strong or moderate inducers or inhibitors of the CYP3A family of CYPs are generally prohibited as concomitant medications with TAK-981. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A activity. Appropriate medical judgment is required. Please contact the sponsor's medical monitor with any queries.

Drugs Inducing or Inhibiting CYP3A Metabolism That are Prohibited Concomitant Medications With TAK-981

Strong CYP3A Inducers [a]	Strong CYP3A Inhibitors [b]
apalutamide	boceprevir
carbamazepine	clarithromycin
enzalutamide	cobicistat
mitotane	danoprevir and ritonavir
phenytoin	elvitegravir and ritonavir
rifampin	grapefruit juice
St John's Wort	idelalisib
	indinavir and ritonavir
	itraconazole
	ketoconazole
	lopinavir and ritonavir
	nefazodone
	nelfinavir
	paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
	posaconazole
	ritonavir
	saquinavir and ritonavir
	telaprevir
	telithromycin
	tipranavir and ritonavir
	troleandomycin
	voriconazole
Moderate CYP3A Inducers [a]	**Moderate CYP3A Inhibitors [b]**
bosentan	aprepitant
efavirenz	ciprofloxacin
etravirine	conivaptan
phenobarbital	crizotinib
primidone	cyclosporine
	diltiazem
	dronedarone
	erythromycin
	fluconazole
	fluvoxamine
	imatinib
	tofisopam
	verapamil

CYP: cytochrome P-450; FDA: Food and Drug Administration.
[a] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table 3-3 (accessed 26 August 2021).
[b] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table 3-2 (accessed 26 August 2021).

Appendix F Examples of Clinical Inhibitors of Pgp

Drugs listed below that are inhibitors of Pgp are generally prohibited as concomitant medications with TAK-981.

Transporter	Gene	Inhibitor
Pgp	ABCB1	amiodarone carvedilol clarithromycin dronedarone itraconazole lapatinib lopinavir and ritonavir propafenone quinidine ranolazine ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir verapamil

Source: fda.gov/fddrugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2 (accessed 06 August 2021).

Pgp: P-glycoprotein.

Appendix G Examples of QTc Interval-Prolonging Agents (Phase 1 Only)

Common concomitant medications can prolong the QT interval (eg, antiemetics, antifungals, quinolone antibiotics). Electrolyte disturbances such as hypokalemia and hypomagnesemia caused by GI toxicities may also increase the risk for QT prolongation. The use of drugs known to prolong the QTc interval should not be initiated on C1D1, but will be allowed from C1D2 onwards.

The drugs noted in the table below are examples of only some of the more common drugs and may not be comprehensive. It is the investigator's responsibility to ensure that drugs under consideration have not been newly identified as causing QT prolongation. The website crediblemeds.org provides a list of drugs known to cause QT prolongation that may be used as a guide for healthcare providers.

Patients taking such drugs need not stop if their baseline QTc <480 ms.

Drug Class	Examples of Drugs That Increase Risk of TdP, Name (Brand Name)
Antiarrhythmic	amiodarone (Cordarone, Pacerone) bepridil (Vascor) disopyramide (Norpace) dofetilide (Tikosyn) flecainide (Tambocor) ibutilide (Corvert) procainamide (Pronestyl, Procan) quinidine (Cardioquin, Quinaglute) sotalol (Betapace)
Antibiotic	azithromycin (Zithromax) clarithromycin (Biaxin) erythromycin (Erythrocin, EES) moxifloxacin (Avelox) pentamidine (NebuPent, Pentam) sparfloxacin (Zagam)
Anticancer	arsenic trioxide (Trisenox) vandetanib (Caprelsa)
Antidepressant	citalopram (Celexa)
Antiemetic [a]	domperidone (Motilium) droperidol (Inapsine) ondansetron granisetron
Antihistamine	astemizole (Hismanal) terfenadine (Seldane)
Antilipemic/ Hypercholesterolemia	probucol (Lorelco)
Antimalarial	chloroquine (Aralen) halofantrine (Halfan)
Antipsychotic	chlorpromazine (Thorazine) haloperidol (Haldol) mesoridazine (Serentil) pimozide (Orap) thioridazine (Mellaril)

Drug Class	Examples of Drugs That Increase Risk of TdP, Name (Brand Name)
Gastrointestinal stimulant/Heartburn	cisapride (Propulsid)
Opiate agonist	levomethadyl (Orlaam) methadone (Dolophine, Methadose)

QTc: corrected QT interval; TdP: torsade de pointes.

[a] Palonosetron is permissible antiemetic.

Appendix H Bayesian Logistic Regression Model

It is anticipated that up to approximately 180 patients will be enrolled in this study including the dosing-escalation phase (up to approximately 35 patients) and efficacy evaluation phase (up to approximately 145 patients).

An adaptive BLRM with overdose control will be used to guide dose escalation starting with the second dose level. BLRM with overdose control principle (Babb et al. 1998; Neuenschwander et al. 2008) informs dose-escalation decisions and MTD estimation, along with consideration of other safety, clinical, PK, and pharmacodynamic data.

The 2-parameter logistic regression model used is as follows:

$\text{logit}(\pi_i) = \log(\alpha) + \beta \log\left(\frac{dose_i}{dose_{ref}}\right), \alpha > 0, \beta > 0$ where π_i is the DLT rate for dose I and $dose_{ref}$ is a reference dose. A quantile-based, weakly informative, bivariate normal prior will be used for ln(α) and ln(β). This prior will be assigned based on pre-study estimates of median DLT rate (0.011,0.021, 0.053, 0.084, 0.105, 0.126, 0.210, 0.263, 0.315, and 0.630) at provisional dose levels (3,6, 10, 15, 25, 40, 60, 90, 120, and 160 mg), as described in Neuenschwander 2008 (Neuenschwander et al. 2008).

The model will be updated after each group of approximately 3 patients are enrolled in the current dose level. Each subject will participate in only 1 dose cohort. A cohort size other than 3 may also be considered as appropriate. For each subsequent dose level after the initial dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.16]: underdosing.
- [0.16, 0.33]: target toxicity.
- [0.33, 1.00]: excessive toxicity.

The next recommended dose will be selected as described in Section 8.5.

The simulation to evaluate the operating characteristics is performed based on provisional dose levels (3, 6, 10, 15, 25, 40, 60, 90, 120, and 160 mg). The cohort size of 3 is assumed in the simulation. The simulation is performed based on 6 scenarios of the assumed true DLT rates at dose levels (3, 6, 10, 15, 25, 40, 60, 90, 120, and 160 mg), representing various distributions of toxicity across dose levels, detailed as shown in Table H-1.

Table H-1 Dose-Escalation Simulation Study of the Probability of DLT

	True P(DLT) at Each Scenario					
Dose Level	**1**	**2**	**3**	**4**	**5**	**6**
3 mg [a]	0.001	0.005	0.01	0.08	0.25	0.50
6 mg	0.005	0.01	0.02	0.12	0.31	0.55
10 mg	0.015	0.03	0.07	0.19	0.45	0.60
15 mg	0.03	0.05	0.12	0.25	0.50	0.65
25 mg	0.04	0.07	0.19	0.30	0.55	0.70
40 mg	0.05	0.10	0.22	0.45	0.60	0.75
60 mg	0.06	0.13	0.25	0.50	0.70	0.80
90 mg	0.08	0.17	0.28	0.60	0.80	0.90
120 mg	0.10	0.21	0.45	0.70	0.90	0.95
160 mg	0.11	0.25	0.60	0.75	0.99	0.99

DLT: dose-limiting toxicity; P(DLT): probability of a DLT at each dose level.
[a] Starting dose.

The trend of the dose-DLT relationship becomes steeper and MTD is reached earlier from Scenario 1 to Scenario 6. The operating characteristic results are shown in Table H-2. In Scenario 1 where all true DLT rates are below 0.33, the probabilities of recommending the highest dose level (160 mg) and the second highest dose level (120 mg) are 30.4% and 53.6%, respectively. In Scenario 1, the average number of patients required is approximately 31.7 with 1.6 DLTs expected on average. The true DLT rates in Scenario 2 increase faster than Scenario 1 but are still all below 0.33, and the BLRM has 78.3% chance of successfully recommending target dose levels. The average number of patients required is approximately 30.8, with approximately 3 DLTs expected on average. In Scenario 3, there is 5.4% chance of recommending a lower dose as MTD, 89.7% chance of successfully recommending target dose levels. The average number of patients required is approximately 27.6, with approximately 4.3 DLTs expected on average. In Scenario 4, with further faster increase of DLT rate over doses, there is a 73.1% probability of recommending target dose levels, whereas the probability of recommending toxic doses is 12.8%. The average number of patients required is approximately 22.8 with 5.2 DLTs expected on average. In Scenario 5, there is 46.2% chance of claiming the target doses as MTD, 14.2% chance of recommending a toxic dose, and approximately 39.6% chance of claiming all doses are toxic. Most of the patients (around 70.7%) do not receive doses above the MTD dose. The average number of patients required is approximately 13.5 with 4.4 DLTs expected on average. In Scenario 6 when all doses are toxic, there is a 92.7% chance of successfully claiming all doses are toxic. The average number of patients required is approximately 6 and 3.1 DLTs are expected on average.

The accuracy of the BLRM recommendation relies on the true DLT rate; thus, the safety, clinical, PK, and pharmacodynamic data evaluation are combined to support the dose escalation. As an example, a hypothetical dose escalation step is shown in Table H-3 to illustrate how BLRM guides dose escalation.

Table H-2 Operating Characteristics for BLRM Dose-Escalation Rule

	Probability of Recommending [a]:			Average Proportion of Patients Receiving [a]:			Average Number of Patients	
Scenario	Low Dose	Target Dose	High Dose	Low Dose	Target Dose	High Dose	Per Study	Experiencing DLT Per Study
1	100%	NA	NA	100%	NA	NA	31.7	1.6
2	21.7%	78.3%	NA	72.6%	27.4%	NA	30.8	3.0
3	5.4%	89.7%	4.8%	45.5%	50.8%	3.5%	27.6	4.3
4 [a]	11.0%	73.1%	12.8%	33.1%	54.3%	12.8%	22.8	5.2
5 [b]	NA	46.2%	14.2%	NA	70.7%	29.2%	13.5	4.4
6 [c]	NA	NA	7.3%	NA	NA	100%	6.0	3.1

BLRM: Bayesian logistic regression modeling; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; NA: Not available.

Low Dose = true DLT rate is [0, 0.16]; Target Dose = true DLT rate is [0.16, 0.33]; High Dose = true DLT rate is [0.33, 1.00].

[a] Probability of 3.1 % to claim all doses are toxic.

[b] Probability of 39.6% to claim all doses are toxic.

[c] Probability of 92.7% to claim all doses are toxic.

Table H-3 Hypothetical Dose-Escalation Step

Step	Dose (mg)	#Patients	#DLTs	Next Recommended Dose (mg)
1	3	3	0	6
2	3	3	0	
	6	3	1	10
3	3	3	0	
	6	3	1	15
	10	3	0	
4	3	3	0	
	6	3	1	
	10	3	0	10
	15	3	2	
5	3	3	0	
	6	3	1	
	10	6	1	
	15	3	2	10 mg is claimed as the MTD

BLRM: Bayesian logistic regression modeling; DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

In addition, BLRM is flexible in handling late-onset toxicities and can be fed with events meeting DLT criteria but occurring in later cycles to modulate dose escalation, as needed. The DLT information from a single-agent study may also be used in the dose-escalation phase as prior information for the BLRM.

Appendix I Rituximab Prescribing Information

accessdata.fda.gov/drugsatfda_docs/label/2019/103705s5454lbl.pdf (Rituxan (rituximab) Injection for Intravenous Use 2019)

Appendix J Methods of Contraception Considered to be Effective

A. Acceptable Methods Considered Highly Effective

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

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

B. Methods That Are Considered Less Highly Effective

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

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

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

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

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

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

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

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

Appendix K Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of TLS

Section 1: First Dose of Rituximab

Within the first 24 hours after either the first dose, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional rituximab doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.

Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any patient hospitalized prophylactically or in response to laboratory changes.

IV fluids (eg, dextrose 5% in half-normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target, 150 to 200 mL/h; not <50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.

Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1-hour immediately (STAT).

Vital signs should be taken at time of all blood draws or any Intervention.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be per institutional protocols.

In addition to the recommendations in the table below:

For potassium increase ≥0.5 mmol/L from baseline, or any value >5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1-hour STAT and follow first guideline.

For phosphorus increase of >0.5 mg/dL AND >4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1-hour STAT.

Abnormality	Management Recommendations (Cairo and Bishop 2004; Coiffier et al. 2008)
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits)	Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still <ULN, manage as per potassium ≥ULN. Otherwise recheck in 1 hour. Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis. At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still within normal limits, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and, Creatinine must be rechecked within 24 hours.
Potassium >ULN	Perform STAT ECG and commence telemetry. Nephrology notification with consideration of initiating dialysis. Administer kayexalate 60 g (or resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer calcium gluconate 100-200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours, if no other evidence of tumor lysis.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. Administer kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 to 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT.

Abnormality	Management Recommendations (Cairo and Bishop 2004; Coiffier et al. 2008)
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	Consider rasburicase (0.2 mg/kg as an IV infusion over 30 minutes). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	Administer rasburicase (0.2 mg/kg as an IV infusion over 30 minutes). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Consult Nephrology (or other acute dialysis service). Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. Telemetry. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥25% from baseline	Start or increase rate of IV fluids. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours STAT.

ECG: electrocardiogram; IV: intravenous; STAT: within 1-hour within 1-hour; ULN: upper limit of normal.

Appendix L Definition of TLS

The following features are used to define TLS:

	Parameter	Value
Laboratory TLS	Uric acid	≥476 µmol/L
(TWO of)	Potassium	≥6.0 mmol/L
	Phosphorus	≥1.45 mmol/L
	Calcium (corrected)	≤1.75 mmol/L
Clinical TLS	Renal insufficiency (increase of 0.3 mg/dL in creatinine)	
(Lab TLS + one of)	Cardiac arrhythmias	
	Sudden death	
	Seizures	

TLS: tumor lysis syndrome.

Appendix M Protocol History

Date	Amendment Number	Region
20 May 2022	Amendment 8	Global
04 October 2021	Amendment 7	Global
02 September 2021	Amendment 6	Global
31 March 2021	Amendment 5	Global
20 January 2021	Amendment 4	Global
18 June 2020	Amendment 3	Global
27 January 2020	Amendment 2	Global
19 July 2019	Amendment 1	Global
04 June 2019	Original protocol	United States and Canada

Rationale for Amendment 7

This section describes the changes to the protocol incorporating Amendment 7.

The primary reason for this amendment was to correct the typographical error in Appendix A Schedule of Events (SOE) Table A-1 SOE for Phase I.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0 STUDY SUMMARY	Changed collection of overall survival information from "every 3 months" to "every 12 weeks".	Typographical error correction.
2	Section 4.2.2 Nonclinical Pharmacology	Corrected the 50% inhibitory concentration value for inhibition of dopamine uptake.	Correction done to align with the investigator's brochure.
3	Section 4.4.2.1 Tumor Biopsies	[redacted]	[redacted]
4	Section 4.2.5 Clinical Experience	Corrected the number of patients receiving TAK-981 as part of a combination regimen.	Typographical error correction.
5	Section 5.1.3 Additional/Exploratory Objectives	[redacted]	[redacted]
6	Section 5.2.3 Additional/Exploratory Endpoints	[redacted]	Typographical error correction.

Protocol Amendment 7			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7	Section 6.2 Phase 1 Study Design Appendix A Schedule of Events Table A-1 SOE for Phase 1	Corrected dosing regiment of rituximab administration during the study.	Typographical error correction.
8	Section 6.4 Number of Patients and Sites	Modified description of countries included for conduct of study.	Modification done to align with details in study summary.
9	Table 6.a Primary and Secondary Endpoints for Disclosures	Corrected definition of primary endpoint of phase 2.	Typographical error correction.
10	Section 9.4.9 Pregnancy Test	Corrected timepoint for conducting pregnancy test.	Typographical error correction.
11	Section 9.9 Posttreatment Follow-up Assessments	Correction done in timepoint for progression-free survival visit.	Typographical error correction.
12	Table A-1 SOE for Phase 1	Added "X" at Cycle 1, Day 15 for complement serum proteins.	Typographical error correction.
13	Table A-2 SOE for Phase 2	Added "X" at screening for viral serologies.	Typographical error correction.
14	[redacted]	Added text to footnote b.	[redacted]

Rationale for Amendment 6

This section describes the changes to the protocol incorporating Amendment 6.

The primary reason for this amendment was to update the translational strategy for collection of pharmacodynamic samples in Phase 2.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria	Added the following inclusion criterion: 6. Potassium levels ≥ lower limit of normal (LLN). For potassium > upper level of normal (ULN) discussion with Takeda medical monitor (MM)/designee recommended. Added the following exclusion criterion: 21. Patients who are committed to an institution by virtue of an order issued either by judicial or administrative authorities.	Change made to fulfill Health Authority requirement.
2	Section 4.2.2 Nonclinical Pharmacology	Added clinical C_{max} data from the 1001 trial and updated the cardiovascular risk section with additional in vitro data (hERG and hCav1.2, stem cell derived cardiomyocyte in vitro assay).	Updated pharmacology data.
3	Section 4.2.4 Nonclinical Toxicology Section 4.2.5 Clinical Experience	Added nonclinical toxicology and clinical experience section with data from latest Investigator's Brochure.	Update of nonclinical toxicology data. Update of clinical data.
4	Section 4.4.2.2 Skin Biopsies	No skin biopsies will be performed in Phase 2.	Phase 1 biopsies were sufficient.
5	Section 4.5.1 Potential Effects of TAK-981 Based on TAK-981 Nonclinical and Clinical Studies	Added nonclinical data from latest Investigator's Brochure. Table 4.a, TAK-981 (All Clinical Studies): Most Frequent (≥10% of All Patients) TEAEs	Update of nonclinical and clinical data
6	5.1.3 Additional/Exploratory Objectives	[redacted]	No longer relevant.
7	Section 8.6.3.3 COVID-19 Infection	Added a section describing criteria for restarting study treatment if a patient discontinued study treatment due to coronavirus disease 2019 (COVID-19) infection.	Changes made to fulfill local requirements.
8	Table 9.d Primary Specimen Collection	Deleted Table 9.d Primary Specimen Collection.	Streamlined protocol.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9	Section 9.4.16.1 Tumor Biopsies	Updated the section Fresh Paired Tumor Biopsy to align with requirement to collect tumor biopsies at screening only in Phase 2 (instead of at screening and on-treatment). Biopsy mandate removed from Phase 2.	Update of biomarker samples collected during Phase 2.
10	Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Added a section defining criteria under which patients must discontinue study drug; this section included pregnancy and other criteria previously noted as reasons that treatment may be discontinued.	Changes made to fulfill Health Authority requirements and edits for clarity.
11	Section 9.10 Early Study Termination	Added a section defining possible reasons for study termination.	Changes made to fulfill Health Authority requirements.
12	Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Updated contact information for reporting medication errors.	Administrative update.
13	Appendix A Schedule of Events Table A-1 SOE for Phase 1 Table A-2 SOE for Phase 2 Table A-3 Serial Plasma PK Sampling Schedule to Characterize PK of TAK-981 When Administered in Combination With Rituximab During Dose Escalation Phase 1 Only Table A-4 Sparse Plasma PK Sampling Schedule to Characterize PK of TAK-981 When Administered in Combination With Rituximab During Phase 2 Only Table A 5 [redacted] Table A-6 [redacted]	Updated Appendix A schedule of event (SOE) table numbers as Tables A-1 through A-5 instead of Tables 1 through 5; added Table A-6. Updated Tables A-1 and A-2 to reflect all assessments from screening through follow-up in Phase 1 and Phase 2, respectively. Updated Table A-4 and added Table A-6 to reflect streamlined pharmacokinetic (PK) and pharmacodynamic sample collection strategies, respectively, for Phase 2. [redacted].	Updates of PK pharmacodynamic SOEs to reflect streamlined sample collection strategy in Phase 2 and updates of all SOE tables for consistency, style, and clarity.

Protocol Amendment 6			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14	Appendix E Drugs That Interact With The CYP3A Family of CYPs Appendix F Examples of Clinical Inhibitors of Pgp	Updated citations.	Editorial updates and corrections.
15	Appendix H Bayesian Logistic Regression Model	Updated Appendix H table numbers as Tables H-1 through H-3 instead of Tables 6 through 8.	Editorial update.

Rationale for Amendment 5

This section describes the changes to the protocol incorporating Amendment 5.

The primary reason for this amendment was to provide guidance on coronavirus disease 2019 (COVID-19) vaccination timing and procedures during the study.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Title page Section 2.0 STUDY SUMMARY	Updated sponsor legal entity name.	Correction and alignment with other TAK-981 protocols.
2	Section 2.0 STUDY SUMMARY Main Criteria for Exclusion Section 7.2 Exclusion Criteria.	In Exclusion Criterion 18 in the study summary and body, added an abbreviation for QTcF (Fridericia-corrected QT interval). In Exclusion Criterion 18 in the study summary, deleted the fragment "QT interval with Fridericia correction method;" edited term "QTcT" to "QTc," and added a definition for QTc.	Alignment of exclusion criterion in protocol summary and body.

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
3	Section 4.5.4 Coronavirus Disease 2019 Pandemic	Added a section on benefit/risk assessment of participation in the study during the coronavirus disease 2019 (COVID-19) pandemic, indicating that the benefit/risk assessment remains favorable and that considerations for patient participation should be evaluated by the investigator on a patient by patient basis taking into consideration the current local situation, guidelines, and other recommendations.	Guidance on benefit/risk assessment for patient participation in the study during the COVID-19 pandemic.
4	Section 8.1.3 Additional Instructions for Treatment Administration Appendix A Schedule of Events Table 1 SOE for Treatment Cycle 1 (21-Day Cycle) During Phase 1 and Phase 2 footnote j Table 2 SOEs for Treatment Cycle 2 (21-Day Cycle) Through End of Study footnote h	Added that a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor. Added that if a treatment visit is delayed, associated tests and procedures should also be delayed.	Guidance on COVID-19 vaccination timing and procedures during the study
5	Section 8.7 Excluded Concomitant Medications and Procedures	Added that vaccination during Cycle 1 is not permitted for patients in Phase 1.	Vaccination during Cycle 1 in Phase 1 would confound safety evaluation and determination of dose-limiting toxicities.
6	Section 8.8 Permitted Concomitant Medications and Procedures	Added guidance on timing of COVID-19 vaccination during the study including live attenuated vaccine must be completed at least 4 weeks prior to treatment initiation, vaccination not permitted during Cycle 1 in Phase 1, vaccination to be avoided within ± 3 days of TAK-981 administration, and allowing a 7-day dose delay to accomodate vaccination.	Guidance on COVID-19 vaccination timing and procedures during the study

Protocol Amendment 5			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7	Appendix A Schedule of Events Table 1 SOE for Treatment Cycle 1 (21-Day Cycle) During Phase 1 and Phase 2 footnote e Table 2 SOEs for Treatment Cycle 2 (21-Day Cycle) Through End of Study footnote d	Updated footnotes with additional text as follows: "If alternative more dense dosing schedules for TAK-981 (eg, TAK-981 on Days 1, 4, 8 and 11, or Days 1, 8, and 15 every 21 days), this test, dose administration, or procedure should be performed on dosing days."	Clarification.
8	Appendix A Schedule of Events Table 2 SOEs for Treatment Cycle 2 (21-Day Cycle) Through End of Study	Deleted footnote k and updated subsequent footnote letters.	Correction.
9	Appendix E Drugs That Interact With the CYP3A Family of CYPs	Under strong cytochrome P450 (CYP) 3A inhibitors, corrected spelling of nefazodone and telithromycin, and added clarithromycin. Updated source table number in footnote a and added footnote b to separate sources for CYP3A inducers and inhibitors.	Update to align with current Food and Drug Administration guidance.

Rationale for Amendment 4

This section describes the changes to the protocol incorporating Amendment 4.

The primary reason for this amendment was to allow additional dosing schedules within the dose escalation phase in order to assess the safety and preliminary efficacy of TAK-981 in combination with rituximab.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Title page	Updated sponsor legal entity and added EudraCT number.	Administrative updates.
2	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	In Inclusion Criterion 6, updated screening creatinine clearance requirement to ≥30 mL/min (instead of ≥45 mL/min) per Cockcroft-Gault formula.	The creatinine clearance requirement was lowered based on recent pharmacokinetic (PK) analysis that showed minimal renal elimination of TAK-981.
3	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	In Inclusion Criterion 11, clarified that tumor biopsy collection was for patients in Phase 2, Stage 1.	Clarification.
4	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	In Exclusion Criterion 9, clarified that the washout period for prior anticancer therapy is within 2 weeks or 5 half-lives before dosing, whichever is shorter; the fragment "(up to a maximum of 4 weeks)" was deleted.	Clarification.
5	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Deleted examples of live vaccine from Exclusion Criterion 14.	Clarification.
6	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	In Exclusion Criterion 19, added that the washout period for P-glycoprotein inhibitors is 1 week before TAK-981 dosing.	Clarification.
7	Section 4.2.5 Clinical Experience	Updated clinical section to include text from the latest investigator's brochure (IB) edition (Edition 3, data cutoff 28 June 2020).	Updated clinical data from the IB were available.
8	Section 4.4.1.1 TAK-981 Section 6.2 Phase 1 Study Design Section 8.1 Study Drug Administration Section 8.5 Dose-Escalation Rules Appendix A Schedule of Events	Updated alternative dosing schedules to include Day 1, or Days 1, 4, 8, and 11, or Days 1, 8, and 15 every 21 days.	Update to allow additional dosing schedules within the dose escalation phase in order to assess the safety and preliminary efficacy of TAK-981 in combination with rituximab.
9	Section 8.1.1 Rituximab	Clarified that body surface area used to determine rituximab dosing was to be calculated using the Du Bois formula.	Clarification on method of calculation of body surface area across participating sites.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
10	Section 8.3 Definition of DLT-Evaluable Patients Section 13.1.1 Analysis Sets	Patients who completed all planned TAK-981 infusions (instead of at least 2 TAK-981 infusions) and 3 rituximab infusions were to be considered dose-limiting toxicity (DLT)-evaluable.	Clarification.
11	Table 8.c Dose Modification Guidelines for CRS Table 8.d CRS Management Recommendations	Corrected descriptions in American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grade column in both cytokine release syndrome (CRS) tables to include the erroneously omitted word "hypoxia". Grade 2, 3, and 4 CRS grades were updated to include both hypotension and hypoxia.	Correction.
12	Table 9.a Clinical Chemistry and Hematology Tests	A footnote was added to the table of chemistry and hematology tests to clarify how the units associated with collection of differential laboratory results were to be described.	Clarification.
13	Section 9.4.15.1 Imaging	Text defining the type of imaging assessments required at screening was added to align with the schedule of events.	Alignment with schedule of events.
14	Section 9.4.16.1 Primary Specimen Collection Appendix A Schedule of Events	[redacted]	Clarification on specimen collection during Phase 2.
15	Section 13.3 Determination of Sample Size	[redacted]	Correction of text to align with other TAK-981 protocols.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16	Section 14.1 Study-Site Monitoring Visits	Text was added to allow for potential remote monitoring of sites due to the COVID-19 pandemic.	Clarification.
17	Appendix A Schedule of Events Table 1 SOE for Treatment Cycle 1 (21-Day Cycle) During Phase 1 and Phase 2	The schedule of events for Cycle 1 was updated to remove collection of the sample for immunesafety biomarkers at Cycle 1, Day 8 and to add flexibility for timing of vital sign measurements before and after dosing of each study drug.	Modifications to simplify vital signs assessment and immunesafety parameters across the TAK-981 clinical studies.
18	Appendix A Schedule of Events Table 2 SOEs for Treatment Cycle 2 (21-Day Cycle) Through End of Study	The schedule of events for Cycle 2 and Cycles 3 and subsequent cycles was updated to remove collection of the hematology/chemistry sample on Day 8 of Cycle 3 and subsequent cycles, to add collection of immunesafety markers at end of treatment, [redacted] and to add flexibility for timing of vital sign measurements before and after dosing of each study drug.	Modifications to simplify vital signs assessment and central and local laboratory assessments across the TAK-981 clinical studies.
19	Appendix A Schedule of Events Table 5 TAK-981-1501: Biomarker Sample Collection	[redacted] collection of selected samples pre-rituximab dosing was added.	Modifications to align central laboratory assessments across the TAK-981 clinical studies.
20	Appendix E Drugs That Interact With the CYP3A Family of CYPs	The list of cytochrome P450 (CYP)3A inhibitors and inducers was updated based on the most recent recommendations from Food and Drug Administration (FDA) (03/06/2020).	Alignment with recent FDA recommendations.
21	Appendix H Bayesian Logistic Regression Model	Renumbered tables and deleted 2 references included in the appendix.	Editorial changes.

Rationale for Amendment 3

This document describes the changes to the protocol incorporating Amendment 03.

The primary reason for this amendment was to incorporate select CD20 positive non-Hodgkin lymphoma (NHL) types and indications in Phase 2 portion to assess the preliminary efficacy of TAK-981 in combination with rituximab in the clinical trial design.

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 M.

Changes in Amendment 3

1. Updated information of the preliminary clinical experience.
2. Changed the title of the study from Phase 1b/2 to Phase 1/2.
3. Modified the Phase 2 patient population.
4. Added text to further describe the study design.
5. Added at least 30 additional recruiting sites and clarified that the study may be conducted outside of North America.
6. Modified Section 6.3 to describe Phase 2 treatment cohorts.
7. Modified Section 6.5.2 to extend the duration of the study.
8. Added an Independent Data Monitoring Committee (IDMC) to the Phase 2 study.
9. Added an Independent Review Committee (IRC) to the Phase 2 study.
10. Updated study schematic figure with the specific tumor types and indications during Phase 2.
11. Deleted measured creatinine clearance from the inclusion criterion and renal function testing.
12. Modified the inclusion criterion regarding radiologically measurable lesions.
13. Replaced Clinical Study Team (CST) with Study Monitoring Committee (SMC), and added a description of the SMC.
14. Removed LYRIC criteria for the evaluation of response.
15. Changed the window for image testing from +10 days to ±7 days.
16. Modified the coagulation testing and urinalysis window period on Cycle 1 Day 1.
17. Changed the tumor and skin biopsy window.
18. Updated Adverse Event (AE) definition.
19. Updated serious adverse event (SAE) definition.
20. Modified language to perform either serum or urine pregnancy test for women of childbearing potential at screening, Day 1 of each cycle, and at the end-of-treatment (EOT) visit.
21. Amended the statistical description of determination of sample size for Phase 2.
22. Modified language to clarify risks and prophylaxis of patients with lymphopenia.
23. Modified the length of infusion time.
24. Added a permitted concomitant treatment.

25. Clarified tumor and skin biopsy inclusion criteria.
26. Modified the starting dose based on emerging safety data from the TAK-981-1002 single-agent study.
27. Modified the staggering period within each cohort in dose escalation from 7 days to 72 h.
28. Modified the grading of cytokine release syndrome (CRS) to ASTCT Consensus Grading for CRS.
29. Updated information on Diffuse Large B-cell lymphoma.
30. Updated study objectives and endpoints.
31. Clarified exclusion criteria for patients that have undergone ASCT or cellular therapy.
32. Added text on alternative dosing schedules for TAK-981.
33. Added timepoints for serum and plasma sample collection.
34. Corrected the list of moderate CYP3A inhibitors and inducers in Appendix E.

Rationale for Amendment 2

This document describes the changes to the protocol incorporating Amendment 02.

The primary reason for this amendment was to incorporate recent requirements by the Food and Drug Administration (FDA) (clarification on dose limiting toxicity [DLT] criteria, addition of reference under statistical considerations for sample size calculation, and addition of appropriate language for safety procedures in tumor biopsies).

The dose escalation of TAK-981 as single agent in the first-in-human (FIH) study (Study TAK-981-1002) in patients with solid tumors or lymphoma is advancing fast. The sponsor now has more insight on dose escalation steps from the safety and pharmacodynamic data available from the FIH study, so the dose escalation steps are also refined in this amendment.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purpose only.

For specific descriptions of text changes and where the changes are located, see Appendix M.

Changes in Amendment 2

1. DLT definitions: In response to FDA's request for clarifying the DLT criteria due to inconsistency in DLT definitions in the Study Summary and Section 8.2, current language was incorporated in the Study Summary and Section 8.2 of the protocol amendment.
2. Corrected the typographical error in inclusion criteria no. 8; replaced "ECG" (electrocardiogram) with "echocardiogram".
3. Added statement in inclusion criteria no. 11, that for fresh tumor biopsies, the lesion must be accessible for a low risk biopsy procedure (those occurring outside the brain, lung/mediastinum, and intra-abdominal, or obtained with endoscopic procedures beyond the stomach or bowel).

4. Added hematology and chemistry laboratory assessments on Cycle 1 Day 1 as they are required to evaluate the suitability of TAK-981 dosing.
5. Removed window periods for tumor lysis syndrome (TLS)-related laboratory assessment.
6. Added that from Cycle 2 onwards, serum or urine pregnancy test will be performed for women of childbearing potential on Day 1 of each cycle.
7. [redacted]
8. Stated in dose escalation (phase 1b) that the selection of the next recommended dose will be determined by the clinical study team (CST) with Bayesian Logistic Regression Modeling (BLRM) recommendations, and consideration of safety, pharmacokinetic (PK), and pharmacodynamic data, including the emerging safety, PK and pharmacodynamic data from the FIH study (TAK-981-1002).
9. Added a reference for Simon's 2-stage design for sample size determination.
10. Added window periods to biomarkers sample collection times in Schedule of Events' Table for Screening, Cycle 1 and 2 Biomarker Sample Collection.
11. Corrected the typographical error about patient population in Study Summary, to be consistent with inclusion criteria.
12. Amended language for laboratory assessments under TLS management, that post dose blood chemistries will be monitored in hospitalized patients "due to high risk TLS".
13. [redacted]
14. Changed AUC_{last} to AUC_t in section for PK analysis, to have consistent use of term "AUC_t".

Rationale for Amendment 1

This document describes the changes to the protocol incorporating Amendment 01. The primary reason for this amendment is to modify the conditions for the starting dose.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purpose only.

For specific descriptions of text changes and where the changes are located, see Appendix M.

Changes in Amendment 1

1. Stated that a starting dose of TAK-981 that is greater than 3 mg may be considered if emerging safety data from the ongoing TAK-981-1002 single agent study supports it, and that alternative dosing schedules may be investigated.
2. Added that the approximately 34 patients in the phase 1b part of the study must be evaluable for dose-limiting toxicities, and that the approximately 56 patients in the phase 2 part of the study should be response evaluable.

3. Increased the number of sites to approximately 9 sites in phase 1b and up to approximately 20 sites total in North America and/or globally.
4. Added language regarding adequate hydration.
5. Added an appendix that defines tumor lysis syndrome (TLS).
6. Added statement that, for laboratory assessments, blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first rituximab dose, and that electrolyte abnormalities should be corrected.
7. Added statement that for patients who show evidence of prior hepatitis B infection (hepatitis B surface antigen [HBsAg] positive [regardless of antibody status] or HBsAg negative but anti-hepatitis B core antibody positive), they should consult with physicians with expertise in managing hepatitis B regarding monitoring.
8. Added that hematology/chemistry assessments should be made at end of treatment.
9. Added an appendix: Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of TLS.
10. Modified inclusion criterion number 3 to require only 1 prior systemic therapy instead of 2.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	25-May-2022 21:19 UTC
[redacted]	Clinical Pharmacology Approval	26-May-2022 14:41 UTC
[redacted]	Clinical Science Approval	27-May-2022 12:41 UTC
[redacted]	Biostatistics Approval	27-May-2022 15:08 UTC