Clinical Study Protocol

NCT Number: NCT03648372

Title: An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies

Study Number: TAK-981-1002

Document Version and Date: Amendment 7.0, 09 November 2021

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

An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy, and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies

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-981-1002

EudraCT Number: 2020-003947-27

Compound: TAK-981

Date: 09 November 2021 **Amendment Number:** 7

Date	Amendment Number	Amendment Type	Region
09 November 2021	Amendment 7	Substantial	Global
14 December 2020	Amendment 6	Substantial	Global
28 August 2020	Amendment 5	Substantial	Global
10 April 2020	Amendment 4	Substantial	United States and Canada
31 March 2020	Amendment 3	Substantial	United States and Canada
26 March 2019	Amendment 2	Substantial	United States and Canada
10 July 2018	Amendment 1	Nonsubstantial	United States and Canada
07 May 2018	Initial protocol	Not applicable	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],
Oncology Clinical Research
(or designee)

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

[redacted], PhD Date
[redacted],
Quantitative Clinical Pharmacology
(or designee)

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

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.
- 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)

1.3 Protocol Amendment 7 Summary of Changes

Protocol Amendment 7 Summary and Rationale:

This section describes the changes to the protocol incorporating Amendment 7. The primary reason for this amendment was to incorporate updated language around pregnancy and lactation to align with the IB.

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.

Protocol Amendment 7			
Summary of Changes Since 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 5.1.2 Secondary Objectives Section 5.2.2 Secondary Endpoints Table 6.a Primary and Secondary Endpoints for Disclosures	Deleted overall response rate (ORR) from secondary objective/endpoint in Phase 2.	Correction: ORR is the primary endpoint, not a secondary endpoint, for Phase 2.
2	Section 4.2.4 Preliminary Clinical Experience	Added a clinical experience section with data from the latest Investigator's Brochure (IB).	Update of the clinical data.
3	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Table 6.a Primary and Secondary Endpoints for Disclosures	Deleted overall survival (OS) from the list of endpoints to be assessed by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) criteria for solid tumors or Lugano classification for lymphomas.	Correction: OS is not assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas.
4	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 8.5 Precautions and Restrictions Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Updated the duration of the contraception and pregnancy reporting period from 120 days to 6 months.	Alignment with the IB.
5	Section 4.4.1.1 Lymphoid and Hematopoietic Effects	Updated the language around lymphoid and hematopoietic effects.	Alignment with other TAK-981 protocols.
6	Section 4.4.1.2 Effects in Renal Pelvis	Updated the language around effects in the renal pelvis.	Alignment with other TAK-981 protocols.

Protocol Amendment 7			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7	Section 4.4.1.4 Injection Site Reactions	Updated the language around injection site reactions.	Alignment with other TAK-981 protocols.
8	Section 4.4.1.5 Reproductive and Development Toxicity	Updated the language around reproductive and development toxicity.	Alignment with other TAK-981 protocols.
9	Section 4.4.2 COVID-19 Pandemic	Added information about the benefit-risk assessment regarding study participation.	Updated information.
10	Section 5.2.2 Secondary Endpoints	Added time to response (TTR) to a Phase 2 secondary endpoint.	Correction because TTR is listed elsewhere in the Phase 2 secondary endpoints.
11	Section 6.1.2 Phase 2 Expansion in Select Cancer Indications	Added information on recommended Phase 2 dosing.	Update of the clinical information.
12	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Updated the exclusion criteria to clarify that patients should discontinue using cytochrome P450 (CYP)3A4/5 and P-glycoprotein inhibitors at least 1 week before starting TAK-981 therapy.	Alignment with other TAK-981 protocols.
13	Section 8.2 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts Section 8.4 Permitted Concomitant Medications and Procedures	Added information regarding COVID-19 vaccination.	Updated information.
14	Table 8.b General Dose Modification Recommendations for TAK-981 Nonhematologic Drug-Related AEs	Clarification added for discontinuing treatment if Grade ≥3 prolongation of the QT interval with Fridericia correction method occurs.	Alignment with other TAK-981 protocols.
15	Section 8.5 Precautions and Restrictions	Updated the language around pregnancy and lactation.	Alignment with the IB.

Protocol Amendment 7			
Summary of Changes Since Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
16	Section 9.4.1.16.1 Primary Specimen Collection	Added a statement, "Collection of samples [redacted] are dependent on local guidelines and regulations (including feasibility of sample export), as well as IRB [institutional review board]/(independent ethics committee) IEC approval."	Added to avoid possible protocol deviations due to under certain circumstances, [redacted] could not be collected.
17	Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Updated the directions for reporting adverse events of special interest.	Alignment with company policy and regulatory agency guidance.
18	Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Updated contact information for reporting medication errors.	Administrative update.
19	Appendix A SOE	Updated the electrocardiography schedule.	Alignment with other TAK-981 protocols.
20	Appendix E Drugs that Interact With the CYP3A Family of CYPs	Removed "grapefruit" from the list of prohibited concomitant medications to align with the sources listed in the table footnote.	Correction.
21	Appendix E Drugs that Interact With the CYP3A Family of CYPs	Added clarithromycin, idelalisib, nefazodone, and nelfinavir to align with the sources listed in the table footnote.	Update.
22	Appendix F Examples of Clinical Inhibitors of P-gp	Corrected the source	Correction

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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: An Open Label, Dose-Escalation, Phase 1/2 Study to Evaluate the Safety, Tolerability, Preliminary Efficacy, and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies	**EudraCT No.:** 2020-003947-27
Study Number: TAK-981-1002	**Phase:** 1/2

Study Design:

This is a Phase 1/2, open-label, dose escalation and dose expansion study designed to evaluate safety, tolerability, preliminary efficacy, and pharmacokinetics (PK) of single-agent TAK-981 in adult patients with advanced or metastatic solid tumors or relapsed/refractory hematologic malignancies.

The study will be conducted in 2 main parts:

1. Phase 1 dose escalation, guided by Bayesian logistic regression modeling (BLRM), in patients with solid tumors or lymphomas.
2. Phase 2 cancer treatment dose expansion with 6 treatment arms: 3 with select solid tumor indications and 3 with CD20+ relapsed/refractory non-Hodgkin lymphoma (NHL) indications.

The study will consist of a screening period (Days -28 to -1), a treatment period, an end-of-treatment visit up to 30 (+10) days after the last dose occurring when treatment is discontinued for any reason, and a posttreatment follow-up period lasting for a maximum of 12 months for each patient who discontinued TAK-981 for reasons other than progressive disease in dose escalation, to monitor survival status after their last dose of TAK-981. 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 for up to 1 year or until confirmed disease progression, unacceptable toxicity, or any criterion for withdrawal from the study or discontinuation of study drug 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.

In Phase 1 (dose escalation), patients will be treated in cohorts with increasing doses of TAK-981, administered as a 1-hour intravenous (IV) infusion on Days 1, 4, 8, and 11 of a 21-day cycle until a discontinuation criterion is met. If clinical safety, PK, and pharmacodynamics are supportive, the protocol schedule can be modified to evaluate a less intensive administration of TAK-981 (eg, Day 1; Days 1 and 8; or Days 1, 8, and 15 in 21-day cycles). Dose escalation intervals progress from 3 mg to 160 mg (with a provision of a dose level -1 of 1 mg). Patient enrollment will be staggered between the first and second patients 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 the Day 4 visit 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 may not be required if there are no clinically significant safety findings suggestive of infusion reaction or cytokine release syndrome (CRS).

Dose escalation of TAK-981 will be cohort-based with an adaptive design using BLRM. Approximately 50 patients will be enrolled until the recommended Phase 2 dose (RP2D) of TAK-981 is identified. Single-agent RP2D could be based either on the maximum tolerated dose (MTD) based on the observation of dose-limiting toxicities (DLTs) or a biologically effective dose (BED) that is ≤MTD.

Once the RP2D is defined, Phase 2 of the study will explore the efficacy and safety of TAK-981 in patients with select cancers. The following cohorts will be enrolled:

- Cohort A: Nonsquamous non–small cell lung cancer (NSCLC).
- Cohort B: Cervical cancer.

- Cohort C: Microsatellite-stable colorectal cancer (MSS-CRC).
- Cohort D: Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) progressed or relapsed after chimeric antigen receptor (CAR) T-cell therapy.
- Cohort E: Relapsed/refractory DLBCL that have not received prior cellular therapy.
- Cohort F: Relapsed/refractory follicular lymphoma (FL).

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 posttreatment scan (ie, after the first disease assessment, 2 months from Cycle 1 Day 1 [C1D1]). 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 clinical benefit has been observed for patients in the cohort (eg, the majority of patients have recorded stable disease at Week 8 and per investigator assessment are benefiting from treatment), then enrollment into stage 2 may be allowed for this cohort with agreement from participating investigators. 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 had the opportunity complete the 6 months disease assessment.

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.

Primary Objectives:

Phase 1:

- To determine the safety and tolerability of TAK-981 as a single agent in patients with advanced or metastatic solid tumors and lymphomas.
- To establish the RP2D of TAK-981.

Phase 2:

- To evaluate preliminary efficacy of TAK-981 in patients with select solid tumors or relapsed/refractory CD20+ NHL indications.

Secondary Objectives:

Phase 1:

- To assess the preliminary antitumor activity of TAK-981.
- To assess target engagement of TAK-981 (small ubiquitin-like modifier [SUMO]–TAK-981 adduct formation) and SUMOylation pathway inhibition in skin and peripheral blood cells.
- To characterize the PK profile of TAK-981.

Phase 2:

- To evaluate the efficacy of TAK-981 in select solid tumor and CD20+ NHL indications as measured by time to response (TTR), duration of the response (DOR), disease control rate (DCR), time to progression (TTP), and progression-free survival (PFS).
- To evaluate overall survival (OS).
- To evaluate the safety and tolerability of TAK-981.
- To collect plasma concentration-time data for TAK-981.

Subject Population:

Phase 1 and Phase 2: Adult patients ≥18 years old with locally advanced or metastatic solid tumor or relapsed/refractory lymphoma with no standard therapeutic alternative with established clinical benefit.

Number of Subjects:	**Number of Sites:**
Phase 1 dose escalation: ~70 patients Phase 2 cancer treatment expansion: ~132 patients	Approximately 60 sites (United States, Canada, and globally)
Anticipated Dose Levels: 3, 6, 10, 15, 25, 40, 60, 90, 120, and 160 mg of TAK-981. A starting dose level of 1 mg will be used if 3 mg is not tolerated.	**Route of Administration:** IV in 1-hour infusion
Duration of Treatment: Up to 1 year. Patients with clinical benefit can continue treatment if approved by the sponsor.	**Period of Evaluation:** Approximately 48 months.

Inclusion Criteria:

1. Adult male or female patients ≥18 years old.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
3. Patient population for Phase 1 dose escalation:
   a. Have a histologically or cytologically confirmed advanced (local regionally recurrent not amenable to curative therapy) or metastatic solid tumors who have no standard therapeutic option with a proven clinical benefit, are intolerant, or have refused them.

   OR

   b. Have a relapsed/refractory lymphoma not amenable to therapies with proven clinical benefit or who are intolerant or who refuse them. Patients with low-grade lymphomas such as FL, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, and marginal zone lymphomas may not need to exhaust all available therapy. These patients can be enrolled after failure of at least 2 prior systemic therapies, provided that there is not an immediate need for cytoreduction. In these cases, patients who need immediate therapy for tumor bulk are not eligible for this trial.
4. Patient population for Phase 2 dose expansion cohorts:

   Have a histologically or cytologically documented, advanced (metastatic and/or unresectable) cancer as listed below, which is incurable and for which prior standard first-line treatment has failed:

   Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line, standard-of-care treatment unless such treatments were completed less than 12 months before the current tumor recurrence.

   a. Nonsquamous NSCLC that has progressed to 1 prior systemic immune checkpoint inhibitor (CPI)/anti-PD-(1/L1)-containing therapy and no more than 2 lines of therapy. Patients must have not shown evidence of tumor progression during the first 5 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy (cohort A).

      Note: Patients with known driver mutations/genomic aberrations (eg, epidermal growth factor receptor, B-Raf proto-oncogene mutation V600E [*BRAF* V600E], and ROS proto-oncogene 1 [*ROS1*] sensitizing mutations, neurotrophic receptor tyrosine kinase [*NRTK*] gene fusions, and anaplastic lymphoma kinase [*ALK*] rearrangements) must have also shown progressive disease after treatment with a commercially available targeted therapy.

   b. CPI-naïve cervical cancer (squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix) patients who have received no more than 1 prior systemic line of therapy for recurrent or Stage IVB cervical cancer (cohort B).

      Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric-type adenocarcinoma, clear-cell carcinoma, and mesonephric carcinoma. Histologic confirmation of the original primary tumor is required via pathology report.

      Note: First-line treatment must have consisted of platinum-containing doublet. Chemotherapy administered

concurrently with primary radiation (eg, weekly cisplatin) is not counted as a systemic chemotherapy regimen.

c. CPI-naïve MSS-CRC patients who have progressed on no more than 3 chemotherapy regimens (cohort C).

Note: Patients must have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens if indicated.

d. Relapsed/refractory DLBCL progressed or relapsed after a prior CAR T-cell therapy that has received approval by a health authority for the treatment of DLBCL (cohort D).

e. Relapsed/refractory 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 E).

f. Relapsed/refractory 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 F).

5. In Phase 2 only, have at least 1 radiologically measurable lesion based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients with solid tumors or Lugano criteria for lymphoma. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: In Phase 2 stage 1, have an additional lesion for pretreatment and on-treatment biopsy.

6. In Phase 2 stage 1, willing to consent to mandatory pretreatment and on-treatment tumor biopsy.

   Note: For fresh tumor biopsies, the lesion must be accessible for a biopsy procedure as assessed by the investigator.

7. Is willing to provide archival tumor tissue sample, if available.
8. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:

   a. Absolute neutrophil count ≥1.0 × 109/L, hemoglobin ≥85 g/L (red blood cell transfusion allowed ≥14 days before assessment), and platelet count ≥75.0 × 109/L(platelet count ≥50.0 × 109/L is allowed for patients with lymphoma if it is clearly due to marrow involvement with no evidence of myelodysplastic syndrome or hypoplastic bone marrow, if found).

   b. Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN); or total bilirubin <3.0 times the ULN with direct bilirubin within normal range in patients with well documented Gilbert's syndrome.

   c. Serum alanine aminotransferase or aspartate aminotransferase ≤3.0 times the ULN (<5 times the ULN if liver enzyme elevations are due to liver metastases).

   d. Estimated creatinine clearance using the Cockcroft-Gault formula ≥45 mL/min.

9. Recovered to Grade 1 or baseline or established as sequelae from all toxic effects of previous therapy (except alopecia, neuropathy, or autoimmune endocrinopathies with stable endocrine replacement therapy, or bone marrow parameters [any of Grade 1/2 permitted if directly related to bone marrow involvement]).
10. Consented to undergo serial skin punch biopsies (dose escalation only).
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Suitable venous access for safe drug administration and the study-required PK and pharmacodynamic sampling.
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:

    a. Postmenopausal for at least 1 year before the screening visit, or

b. Surgically sterile, or

c. 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 6 months after the last dose of study drug, or

d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], 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 post vasectomy) must agree to 1 of the following:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or

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

Exclusion Criteria:

1. Phase 1 dose escalation and Phase 2 cancer treatment expansion cohorts:
    a. Have received treatment with systemic anticancer treatments or investigational products within 14 days before the first dose of study drug or 5 half-lives, whichever is shorter.

    Note: Low-dose steroids (oral prednisone or equivalent ≤20 mg per day), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed.

    b. Have received extended field radiotherapy ≤4 weeks before the start of treatment (≤2 weeks for limited field radiation for palliation) and have not recovered to Grade 1 or baseline from related side effects of such therapy (except for alopecia).
2. Have a history of uncontrolled brain metastasis. Patients with brain metastases are allowed if they are previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery and the patients are receiving a corticosteroid dose ≤10 mg/day of prednisone equivalent at the time of receiving the first dose of TAK-981. For asymptomatic patients, screening brain imaging is not required.
3. Patient is receiving any live vaccine (eg, varicella, pneumococcus) within 4 weeks of initiation of study treatment.
4. History of any of the following ≤6 months before first dose: congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, severe noncompensated hypertension despite appropriate medical therapy, 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.
5. Baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
6. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of adverse events (AEs) or has compromised ability to provide written informed consent.
7. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
8. History of autoimmune disease requiring systemic immunosuppressive therapy with daily doses of prednisone >10 mg/day or equivalent doses, or any other form of immunosuppressive therapy. Hormone therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered an excluded form of systemic treatment of an autoimmune disease
9. History of immune-related AEs related to treatment with immune checkpoint inhibitors that required treatment

discontinuation.

10. History of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
11. Has evidence of active, noninfectious pneumonitis.
12. Have a significant active infection.
13. Known history of human immunodeficiency virus infection or any other relevant congenital or acquired immunodeficiency.
14. Known hepatitis B virus surface antigen seropositive or detectable hepatitis C infection viral load.

    Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
15. Receiving or requiring the continued use of medications that are known to be strong or moderate inhibitors and inducers of cytochrome P450 (CYP)3A4/5 (Appendix E) or are strong P-glycoprotein (P-gp) inhibitors (Appendix F). To participate in this study, such patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and P-gp inhibitors) before receiving a dose of TAK-981.
16. Patient requires the use of drugs known to prolong corrected QT interval (during History of allogeneic tissue or solid organ transplant.
18. 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.
19. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

Main Criteria for Evaluation and Analyses:

Primary Endpoints

Phase 1:

- Frequency, severity, and duration of treatment-emergent adverse events (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 [1].
- DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- Overall response rate (ORR) (complete response [CR] + partial response [PR]) as defined by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas.

Secondary Endpoints

- PK parameters after the first dose of TAK-981 on C1D1 and Cycle 1, Day 8 (data permitting):
  - Maximum observed plasma concentration (C_{max}).
  - Time of first occurrence of maximum observed plasma concentration.
  - Area under the plasma concentration-time curve from time 0 to the last measurable concentration.
  - Area under the plasma concentration-time curve from time 0 to infinity.
  - Terminal disposition phase half-life.
  - Total clearance (CL) after IV administration.
  - Volume of distribution at steady state after intravenous administration.

Phase 1:

- ORR, DCR, DOR, TTP, and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or 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, TTR, TTP, and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS.

Statistical Considerations:

In Phase 1, dose escalation of TAK-981 will be cohort-based with an adaptive BLRM guided by the 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 of ORR (CR + PR) will be assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas. 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 different hypotheses of ORR for disease-specific cohorts.

Sample Size Justification:

Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts:

It is estimated that up to approximately 70 DLT-evaluable patients will be enrolled in this study for the dose escalation phase (Phase 1).

Once the MTD/BED is defined, up to approximately 132 response-evaluable patients with 6 specified types of solid tumors and lymphomas will be enrolled in parallel in the Phase 2 portion of the study to evaluate the efficacy of TAK-981.

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 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, 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

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem-cell transplantation
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
BED	biologically effective dose
BIW	twice weekly
BLRM	Bayesian logistic regression modeling
BCRP	breast cancer resistance protein
C1D1	Cycle 1, Day 1
C1D8	Cycle 1, Day 8
C2D8	Cycle 2, Day 8
CAR	chimeric antigen receptor
CFR	[United States] Code of Federal Regulations
CL	total clearance
CL_p	plasma clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRA	cytokine release assay
CRC	colorectal cancer
CRS	cytokine release syndrome
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
CV	cardiovascular
CYP	cytochrome P450
DC	dendritic cell
DCR	disease control rate
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response

EC_{20}	concentration producing 20% activation
ECG	electrocardiogram, electrocardiographic, electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
FDA	[United States] Food and Drug Administration
FDG-PET	^{18}fluorodeoxyglucose–positron emission tomography
FIH	first-in-human
FL	follicular lymphoma
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HNSTD	highest nonseverely toxic dose
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IFN	interferon
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
MABEL	minimum anticipated biological effect level
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSS-CRC	microsatellite-stable colorectal cancer
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	overall response rate

OS	overall survival
PBMC	peripheral blood mononuclear cell
PD-L1	programmed death ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PRR	pattern recognition receptor
QSP	quantitative systems pharmacology
QTc	heart rate–corrected QT interval
QTcF	QT interval with Fridericia correction method
QW	once weekly
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SMC	Safety Monitoring Committee
SOC	standard of care
SOE	schedule of events
STD10	severely toxic dose in 10% of animals tested
STING	stimulator of interferon genes
SUMO	small ubiquitin-like modifier
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time of first occurrence of maximum observed plasma concentration
TEAE	treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state after intravenous administration
WHO	World Health Organization

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 Immunotherapy in Cancer

Immuno-oncology has emerged as the major driver of anticancer therapeutics in both solid tumors and hematologic malignancies. Clinical data from immune checkpoint inhibitors (CPIs), such as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), and programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors have changed the therapeutic paradigm in a growing number of indications. Overcoming T cell inhibition in the tumor microenvironment with CPIs has proven to be a successful strategy to produce long-term benefit in a significant number of patients with metastatic solid tumors.

However, despite these advances, many advanced cancer patients are either refractory to CPIs or relapse after a period of tumor control, eventually succumbing to their disease. Some predictive biomarkers of CPI response (PD-L1 expression, microsatellite instability, or tumor mutational burden) have been clinically validated, but it remains incompletely understood why most human tumors do not respond to CPIs. Evolving data suggest that reduced interferon (IFN) signaling, immune escape through human leukocyte antigen loss, as well as altered antigen presentation may contribute to CPI resistance [2-4]. Furthermore, an emerging consensus acknowledges that CPI resistance (relapse or refractory in nature) may also be driven by tumor immunophenotype, specifically those tumors harboring an immunosuppressive or "immune desert" phenotype.

Accordingly, one possible strategy to overcome these elements of resistance is to stimulate innate immune cells (myeloid cells including antigen-presenting dendritic cells [DCs] and monocytes/macrophages), as well as lymphoid cells and natural killer [NK] cells, to condition the tumor microenvironment, thus turning a "cold" tumor into a "hot" tumor in which adaptive immune responses can be effectively activated.

Type I IFNs, such as IFNα and IFNβ, are potent immunomodulatory cytokines induced early in the innate immune response that act upon multiple cell types to mold both innate and adaptive immunity. They directly enhance NK cell cytotoxicity and stimulate IL-15 production by DCs to promote NK cell activation [5-8]. They also directly act upon T cells to stimulate survival, clonal expansion, and the development of T cell effector function [7,8]. Importantly, type I IFNs play a central role in propagating adaptive immune responses by promoting maturation of DCs and cross-presentation of antigens to T cells [9,10]. Indeed, innate immune responses have been implicated in tumor surveillance, via sensing of tumor DNA through the stimulator of interferon genes (STING)–controlled pathway [11], activation of which induces production of type I IFNs and propagation of an adaptive antitumor response as described above.

4.1.1 Solid Tumors

4.1.1.1 Lung Cancer

Lung cancer is the leading cause of cancer-related mortality worldwide, with 142,670 deaths estimated in 2019 in the United States (US) [12]. More than 80% of lung cancers are classified as

non–small cell lung cancer (NSCLC). Although targeted therapies have redefined treatment options for patients with molecularly defined locally advanced or metastatic NSCLC (eg, epidermal growth factor receptor [*EGFR*]-mutant, anaplastic lymphoma kinase [*ALK*]-rearranged NSCLC), these therapies are ineffective in those whose tumors lack such genetic alterations, who comprise the majority of NSCLC patients. By contrast, immunotherapy has become integrated into the first-line treatment of such patients, which has led to improvements in survival. However, despite the overall survival (OS) benefit of CPI in NSCLC, treatment in the advanced disease setting is palliative.

4.1.1.2 Cervical Cancer

Cervical cancer is the fourth leading cause of cancer-related mortality in women worldwide, with 13,170 new cases and 4250 deaths in 2019 in the US [12]. In contrast to patients with early-stage cervical cancer, the prognosis of patients with recurrent or metastatic disease is poor. Over the past 30 years, cisplatin-based combination chemotherapy has been shown to produce the best progression-free survival (PFS) and median OS: 5 months and 10 to13 months, respectively [13-15]. The addition of bevacizumab to standard first-line chemotherapy significantly improved median PFS (8.2 months vs 5.9 months; hazard ratio [HR], 0.67; 95% CI, 0.54-0.82) and modified OS (17.0 months vs 13.3 months; HR, 0.71; 95% CI, 0.54-0.95) compared with chemotherapy alone. Treatment after platinum failure is a big challenge, and currently available single agents, such as topotecan, vinorelbine, gemcitabine, docetaxel, nab-paclitaxel, and pembrolizumab, have shown unsatisfactory activity.

4.1.1.3 Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death worldwide, with 51,020 deaths estimated during 2019 in the US [12]. Advanced Stage IV metastatic disease is the initial presentation in approximately 25% of patients with CRC, and a further 25% to 50% present with an early-stage disease but go on to develop metastatic disease. Despite the development of several chemotherapy regimens and the addition of EGFR/vascular endothelial growth factor A–directed monoclonal antibodies, the prognosis for patients with metastatic CRC remains poor, with a median 5-year survival of only 12.5% in the US [16].

4.1.2 Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is among the most common cancers in the US and Europe with more than 70,000 and 93,000 new cases diagnosed every year, respectively [17,18]. 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 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 [19]. 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 [20]. 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.

4.1.2.1 Follicular Lymphoma

Indolent NHL represents 40% of all NHL subtypes, with follicular lymphoma (FL) occurring with the greatest frequency [21]. FL presents with a broad spectrum of disease characteristics. Patients 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 [22]. The most common frontline therapies include a combination of alkylators (including cyclophosphamide, doxorubicin, vincristine, and prednisone [or 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 [23]. 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 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 [22,24,25]. 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 [26-28].

4.1.2.2 DLBCL

Aggressive NHL accounts for approximately 30% to 40% of all NHL cases [29], and DLBCL is the most common histological subtype [30]. Combination chemotherapy with the addition of rituximab is standard of care (SOC) for patients with newly diagnosed DLBCL. However, approximately 40% of patients with DLBCL relapse following initial immunochemotherapy [31]. For eligible patients, salvage chemotherapy regimens, such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide) and R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) followed by autologous stem cell transplantation (ASCT), are the treatments of choice for patients with relapsed/refractory disease. Unfortunately, 40% to 50% of patients will not be eligible for ASCT due to chemorefractory disease, and the other 50% who undergo the procedure are at risk of disease relapse and significantly high nonrelapse mortality [32]. For patients with disease relapse following transplant or for patients not eligible for transplant, treatment with CD19-directed chimeric antigen receptor (CAR) T-cell therapy has shown overall response rates (ORRs) of 52% to 82% with a median duration of response (DOR) of >9 months [33,34].

Currently, there is no SOC for patients that are not eligible or progressed after CAR T-cell therapy. Multiple chemotherapy regimens and investigational agents in clinical trials are being used for such patients. However, clinically meaningful benefit is rarely achieved in patients with

progressive disease following multiple regimens. DLBCL therefore remains a significant unmet medical need.

4.2 Background

TAK-981 is an intravenous (IV) first-in-class small molecule inhibitor of SUMOylation, a posttranslational modification that attaches a small ubiquitin-like modifier (SUMO) protein to protein substrates, regulating their activity, subcellular localization and stability [35]. There are 3 functional mammalian paralogues of the SUMO proteins: SUMO1, SUMO2, and SUMO3 [35,36], which are attached to their substrate proteins as monomers (SUMO1) or poly SUMO chains (SUMO2/3). The SUMOylation process is mediated by an enzymatic cascade similar to that described for ubiquitination [35,37]. The SUMO-activating enzyme, consisting of a SUMO-activating enzyme subunit 1/SUMO-activating enzyme subunit 2 heterodimer, binds SUMO, generating a SUMO thioester that is transferred to the sole SUMO-conjugating enzyme (UBC9) in the pathway, following which SUMO is covalently attached to a lysine residue on target proteins through a process facilitated by an E3 ligase. TAK-981 interrupts this cascade by forming an irreversible covalent adduct with SUMO when bound to SUMO-activating enzyme, preventing its transfer to UBC9.

SUMOylation has been reported to regulate cellular processes important for tumor cell proliferation and survival [37,38]. 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 I IFN expression has been demonstrated [39], such that inhibiting SUMOylation by genetic means resulted in enhanced basal expression levels and sensitization of induction of type I IFNs, promoting enhanced innate immune responses to pathogenic stimuli. The sponsor's studies have similarly demonstrated upregulation of Type I IFNs following pharmacological inhibition of SUMOylation with TAK-981 and generation of innate and adaptive antitumor immune responses. Indeed, a key role for Type I IFNs in stimulating anti-tumor immune responses has been documented in work demonstrating that sensing of tumor DNA through the pattern recognition receptor (PRR) pathway, resulting in activation of production of Type I IFNs, plays an important role in tumor surveillance [11].

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 [40]. 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 PRR pathway through administration of agonists (such as the STING 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 [41]. Inhibition of SUMOylation represents a novel therapeutic strategy for initiating type 1 IFN responses and enhancing antitumor immune responses.

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

4.2.1 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 (or UAE), Nedd8-activating enzyme (or NAE), and autophagy related 7 (or ATG7) 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. In ex vivo assays evaluating the activity of TAK-981 on the function of human monocyte derived macrophages (MDMs) and human NK cells (both derived from peripheral blood mononuclear cells [PBMCs]), 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 the activation marker CD69 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 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 induced robust, durable, and dose-responsive inhibition of SUMO2/3 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 potential for TAK-981 to promote type-I-IFN–dependent 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 and/or antibody-dependent cell-mediated phagocytosis provides the mechanistic rationale for this synergistic combination activity.

Ex vivo characterization of mouse bone marrow-derived DCs and human DCs isolated from PBMCs demonstrated that TAK-981 promoted DC maturation as assessed by upregulation of the T cell costimulatory markers CD40, CD80, and CD86. Consistent with these findings, TAK-981 also induced release of type I IFNs and proinflammatory 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 upon twice-weekly (BIW) treatment with TAK-981, but once-weekly (QW) treatment at the same total weekly dose was also typically comparably effective. Rechallenge 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. Blockade of Type I IFN signaling by treatment of wild type tumor-bearing mice with the type I IFN receptor IFNAR1 neutralizing antibody before administration of TAK-981 resulted in complete loss of TAK-981 antitumor activity, indicative of a key role for type I IFN signaling in the antitumor mechanism of action of TAK-981.

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 were 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 was 4.9 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 plasma concentrations (the highest projected plasma at maximum observed plasma concentration [C_{max}] at a human dose of 182 mg is 0.702 μM). Additionally, modulation of these receptors is readily monitorable (eg, altered blood pressure, heart rate, gastrointestinal motility, and 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 and in vivo cardiovascular (CV) assessment indicate that the risk of QT interval prolongation in humans is low. In vivo CV assessment in beagle dogs revealed dose-related increases in heart rate and body temperature from approximately 6 to 24 hours postdose. These finding were not associated with changes in blood pressure or in electrocardiographic (ECG) traces. Based on the currently available nonclinical information, TAK-981 may result in monitorable effects on the CV system (increased heart rate) that may be related to increased body temperature.

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]

[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.

4.2.2 Nonclinical PK

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

- In plasma after single IV administration, TAK-981 showed moderate to high plasma clearance (CL_p) 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 µM 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 P450 (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 of 37.1 µM (CYP1A2), 21.6 µM (CYP2B6), 57.2 µM (CYP2C8), 18.7 µM (CYP2C9), 7.9 µM (CYP2C19), 7.1 µM (CYP2D6), 79.9 µM (CYP3A4/5; midazolam), and 7.9 µM (CYP3A4/5; testosterone). Clinically significant drug-drug interaction (DDI) 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 DDI potential with CYP3A4/5 inhibitors or inducers with TAK-981 as a victim.
- TAK-981 is a substrate of P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP) and is an inhibitor of P-gp (IC_{50} of 30.4 µM) and BCRP (IC_{50} of 24.4 µM). The DDI

potential with P-gp and BCRP substrates with TAK-981 as a perpetrator is low; however, there is a DDI potential with P-gp 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 CL_p 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.

4.2.3 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 with 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 CV assessment study and after repeat once daily or QW dosing. Increased body temperature in the CV 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 once or BIW schedule was demonstrated to be efficacious in mouse models, both once 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. However, 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, patients will be dosed BIW in the Phase 1 clinical trial.

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 with 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), interferon-inducible protein-10 (IP-10) (rats only), and RANTES (rats only) at ≥5 mg/kg (with no increases in cytokines typically associated with cytokine release syndrome [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 nontolerated 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.

TAK-981 was not mutagenic in an in vitro bacterial mutagenesis Ames assay. However, in an in vivo rat bone marrow micronucleus assay, TAK-981 administered on 2 consecutive days increased induction of micronuclei and was therefore considered to be positive for in vivo genotoxicity at ≥5 mg/kg. It was not determined whether TAK-981 induces clastogenic or aneugenic genotoxicity. In compliance with ICH S9 guidance [42], a carcinogenicity assessment is not planned.

Reproductive and developmental toxicity studies have not been conducted. Reproductive tissues (ovaries, uterus, cervix, vagina, testes, epididymis, and prostate gland) 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. TAK-981–related reproductive effects were not observed in these studies. However, in a non–GLP-compliant 7-day repeat dose toxicity study in rats with daily dosing, TAK-981–related reproductive effects included minimal to mild single cell necrosis of epithelium in the prostate gland and epididymis, mild atrophy of prostate epithelium, mild karyomegaly of epididymis epithelium, minimal to mild increases in mitotic figures in the epididymis, moderate to marked increases in debris in the epididymis, and minimal to mild degeneration and necrosis of seminiferous tubules in the testis. Reproductive effects correlated with decreased prostate gland, epididymis, and testis weights. There were no effects on female reproductive tissues in this study. 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), TNFα, IFNg, or granulocyte colony-stimulating factor (G-CSF) levels. TAK-981–related increases in IP-10 levels were noted at ≥0.5 µM (8- to 50-fold compared with 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 as negative.

4.2.4 Preliminary Clinical Experience

TAK-981 is currently being evaluated in this ongoing first-in-human (FIH) Phase 1 study in patients with advanced or refractory solid tumors or lymphomas (Study TAK-981-1002), in 1 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), and in 1 ongoing Phase 1b/2 clinical efficacy and safety study of the combination with pembrolizumab in patients with advanced or metastatic solid tumors.

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. 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 the 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, Table 5.g. Data cutoff date: 28 June 2021.
AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.
AEs graded according to NCI CTCAE Version 5.0.

The TAK-981 studies revealed some pharmacologically active doses at ≥60 mg. In Study TAK-981-1002, pharmacodynamic activity, including SUMO pathway inhibition [redacted], was most consistently detected at doses ≥60 mg. The maximum tolerated dose (MTD) was determined to be 120 mg; the RP2D for single-agent TAK-981 was 90 mg, when administered BIW (Days 1, 4, 8, and 11) in a 21-day cycle. Of the 81 patients, 4 had DLTs, which were reported in the single-agent study: transient Grade 3 serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations at 60 mg BIW; Grade 3 recurrent pneumonitis after a previous pneumonitis with an anti–PD-1 inhibitor at 90 mg BIW; and, 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 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.

Results of the preliminary analysis of available data for the heart rate–corrected QT interval (QTc) are consistent with a low risk of QTc prolongation after IV administration of TAK-981 alone [redacted] or in combination with rituximab at doses of 10 to 90 mg (Study TAK-981-1501).

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

4.2.4.1 Study TAK-981-1002

The TAK-981-1002 study is evaluating the safety, tolerability, and efficacy of TAK-981 at the following dose levels: 3, 6, 10, 15, 25, 40, 60, 90, 120, and 160 mg on Days 1, 4, 8, and 11 every 3 weeks. As of 28 June 2021, a total of 81 patients have been treated with TAK-981. Number of patients enrolled at each dose level and dosage regimen are shown in Table 4.b.

Table 4.b Study TAK-981-1002: Patient Enrollment Per Dose Level

Dose Level of TAK-981	Dosing Schedule	Number of Patients
3 mg	Days 1, 4, 8, and 11	5
6 mg	Days 1, 4, 8, and 11	3
10 mg	Days 1, 4, 8, and 11	4
15 mg	Days 1, 4, 8, and 11	3
25 mg	Days 1, 4, 8, and 11	4
40 mg	Days 1, 4, 8, and 11	4
60 mg	Days 1 and 8	6
60 mg	Days 1, 4, 8, and 11	7
75 mg	Days 1 and 8	6
75 mg	Days 1, 4, 8, and 11	6
90 mg	Days 1 and 8	7
90 mg	Days 1, 4, 8, and 11	8
90 mg	Days 1, 8, and 15	4
120 mg	Days 1 and 8	6
120 mg	Days 1, 4, 8, and 11	8

Source: Investigator's Brochure Edition 4, Table 5.h. Data cutoff date: 28 June 2021.

As of 28 June 2021, 76 (93.8%) of the 81 patients presented with at least 1 TEAE. Table 4.c displays the most common TEAEs reported in ≥10% of patients, regardless of causality. The most commonly reported TEAE was fatigue. Other common TEAEs were nausea, headache, diarrhea, pyrexia, vomiting, dyspnea, and decreased appetite. Grade 1 CRS were reported in 7 patients and 4 patients experienced Grade 2 CRS.

Table 4.c Study TAK-981-1002: TEAEs Reported in ≥10% of Patients

TEAE Preferred Term	Number of Patients (%) Total (N = 81)
Fatigue	34 (42.0)
Nausea	33 (40.7)
Headache	26 (32.1)
Diarrhea	24 (29.6)
Pyrexia	23 (28.4)
Dyspnea	18 (22.2)
Vomiting	18 (22.2)
Decreased appetite	17 (21.0)
Chills	16 (19.8)
Abdominal pain	15 (18.5)
Hypokalemia	15 (18.5)
Oedema peripheral	15 (18.5)
Constipation	12 (14.8)
Abdominal distension	10 (12.3)
Insomnia	10 (12.3)
Anemia	9 (11.1)
Back pain	9 (11.1)
Cytokine release syndrome	9 (11.1)
Dehydration	9 (11.1)
Hypophosphatemia	9 (11.1)

Source: Table 15.3.1.7 Most Frequent (at least 10% of all patients) TEAEs. Data cutoff date: 28 June 2021.
AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.
AEs graded according to NCI CTCAE Version 5.0.

Overall, 43 (53.1%) patients reported Grade ≥3 TEAEs. Most commonly reported Grade ≥3 TEAEs were hypokalemia, anemia, decreased lymphocyte count, abdominal pain, dyspnea, small intestine obstruction, vomiting, and fatigue. Table 4.d describes all that Grade ≥3 TEAEs.

Table 4.d Study TAK-981-1002: Grade ≥3 TEAEs

TEAE System Organ Class Preferred Term	Number of Patients (%) Total (N = 81)
Gastrointestinal disorders	
Abdominal pain	4 (4.9)
Small intestinal obstruction	3 (3.7)
Vomiting	3 (3.7)
Nausea	1 (1.2)
Rectal obstruction	1 (1.2)
Diarrhea	1 (1.2)
Rectal hemorrhage	1 (1.2)
Esophagitis	1 (1.2)
Stomatitis	1 (1.2)
Glossodynia	1 (1.2)
Incarcerated umbilical hernia	1 (1.2)
General disorders and administration site conditions	
Fatigue	3 (3.7)
Pyrexia	1 (1.2)
Performance status decreased	1 (1.2)
Pain	1 (1.2)
Metabolism and nutrition disorders	
Hypokalemia	7 (8.6)
Dehydration	2 (2.5)
Hypercalcemia	1 (1.2)
Hyperuricemia	1 (1.2)
Hyperglycemia	1 (1.2)
Hypomagnesemia	1 (1.2)
Hypophosphatemia	1 (1.2)
Investigations	
Lymphocyte count decreased	5 (6.2)
Blood bilirubin increased	2 (2.5)
Alanine aminotransferase increased	1 (1.2)
Aspartate aminotransferase increased	1 (1.2)
Platelet count decreased	1 (1.2)
Blood creatinine increased	1 (1.2)

Table 4.d Study TAK-981-1002: Grade ≥3 TEAEs

TEAE System Organ Class Preferred Term	Number of Patients (%) Total (N = 81)
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	4 (4.9)
Pneumonitis	2 (2.5)
Pleural effusion	2 (2.5)
Pulmonary embolism	1 (1.2)
Dysphonia	1 (1.2)
Blood and lymphatic system disorders	
Anemia	6 (7.4)
Pancytopenia	1 (1.2)
Thrombocytopenia	1 (1.2)
Infections and infestations	
Cystitis	1 (1.2)
Urinary tract infection	1 (1.2)
Appendicitis	1 (1.2)
Pneumonia	1 (1.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	
Malignant neoplasm progression	1 (1.2)
Pancreatic carcinoma	1 (1.2)
Small cell lung cancer	1 (1.2)
Renal and urinary disorders	
Acute kidney injury	2 (2.5)
Urinary tract obstruction	1 (1.2)
Hematuria	1 (1.2)
Injury, poisoning, and procedural complications	
Fall	1 (1.2)
Lumbar vertebral fracture	1 (1.2)
Vascular disorders	
Hypertension	1 (1.2)
Hypotension	1 (1.2)
Cardiac disorders	
Mitral valve incompetence	1 (1.2)
Hepatobiliary disorders	
Bile duct obstruction	1 (1.2)
Musculoskeletal and connective tissue disorders	
Back pain	1 (1.2)

Table 4.d Study TAK-981-1002: Grade ≥3 TEAEs

TEAE System Organ Class Preferred Term	Number of Patients (%) Total (N = 81)
Nervous system disorders	
Cognitive disorder	1 (1.2)
Peripheral sensory neuropathy	1 (1.2)
Psychiatric disorders	
Confusional state	1 (1.2)
Skin and subcutaneous tissue disorders	
Dermatitis acneiform	1 (1.2)

Source: Table 15.3.1.4 Grade 3 or Higher TEAEs. Data cutoff date: 28 June 2021.
AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.
AEs graded according to NCI CTCAE Version 5.0.

Fourteen (17.3%) patients experienced Grade ≥3 TEAEs that were considered related to TAK-981 as assessed by the investigator. TAK-981–related Grade ≥3 TEAEs were lymphocyte count decreased in 4 (4.9%) patients; hypokalemia and pneumonitis in 2 (2.5%) patients each; and ALT increased, AST increased, platelet count decreased, anemia, pancytopenia, thrombocytopenia, vomiting, stomatitis, cognitive disorder, and dermatitis acneiform in 1 (1.2%) patient each.

Of 65 (80.2%) patients who had discontinued treatment, 8 (9.9%) patients discontinued treatment due to a TEAE. TEAEs that lead to study drug discontinuations were Grade 3 cognitive disturbance and Grade 1 sinus bradycardia in 1 patient, Grade 3 small intestinal obstruction, Grade 3 pneumonitis, Grade 3 bilateral pulmonary embolism, progression of small cell lung cancer, Grade 3 dyspnea, Grade 3 pneumonitis, and Grade 2 fatigue.

All treatment-emergent serious adverse events (TESAEs) are displayed in Table 4.e. Thirty-four (42.0%) of 81 patients experienced TESAEs. Most commonly reported TESAEs were vomiting, small intestinal obstruction, dyspnea, abdominal pain, pneumonia, CRS, and blood bilirubin increased.

Table 4.e Study TAK-981-1002: TESAEs

TEAE System Organ Class Preferred Term	Number of Patients (%) Total (N = 81)
Gastrointestinal disorders	
Vomiting	3 (3.7)
Small intestinal obstruction	3 (3.7)
Abdominal pain	2 (2.5)
Rectal obstruction	1 (1.2)
Rectal hemorrhage	1 (1.2)
Glossodynia	1 (1.2)
Incarcerated umbilical hernia	1 (1.2)
Respiratory, thoracic, and mediastinal disorders	
Dyspnea	3 (3.7)
Pneumonitis	2 (2.5)
Pleural effusion	2 (2.5)
Hypoxia	1 (1.2)
Pulmonary embolism	1 (1.2)
Infections and infestations	
Pneumonia	2 (2.5)
Appendicitis	1 (1.2)
Cystitis	1 (1.2)
General disorders and administration site conditions	
Fatigue	1 (1.2)
Oedema peripheral	1 (1.2)
Pain	1 (1.2)
Injury, poisoning, and procedural complications	
Subdural hematoma	1 (1.2)
Fall	1 (1.2)
Infusion related reaction	1 (1.2)
Lumbar vertebral fracture	1 (1.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	
Malignant neoplasm progression	1 (1.2)
Pancreatic carcinoma	1 (1.2)
Small cell lung cancer	1 (1.2)
Nervous system disorders	
Dizziness postural	1 (1.2)
Presyncope	1 (1.2)
Cognitive disorder	1 (1.2)

Table 4.e Study TAK-981-1002: TESAEs

TEAE System Organ Class Preferred Term	Number of Patients (%) Total (N = 81)
Immune system disorders	
Cytokine release syndrome	2 (2.5)
Investigations	
Blood bilirubin increased	2 (2.5)
Metabolism and nutrition disorders	
Hyperglycemia	1 (1.2)
Dehydration	1 (1.2)
Renal and urinary disorders	
Acute kidney injury	1 (1.2)
Hematuria	1 (1.2)
Cardiac disorders	
Sinus bradycardia	1 (1.2)
Hepatobiliary disorders	
Bile duct obstruction	1 (1.2)
Musculoskeletal and connective tissue disorders	
Back pain	1 (1.2)
Skin and subcutaneous tissue disorders	
Dermatitis acneiform	1 (1.2)

Source: Table 15.3.1.5 TESAEs. Data cutoff date: 28 Jun 2021.
AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TESAE: treatment-emergent serious adverse event.
AEs graded according to NCI CTCAE Version 5.0.

Seven patients (9 events) experienced TESAEs that were considered related to study treatment as assessed by the investigator (1 patient experienced Grade 3 pneumonitis, 1 patient experienced Grade 2 CRS, 1 patient experienced Grade 3 cognitive disorder and Grade 1 sinus bradycardia, 1 patient had Grade 3 dermatitis acneiform, 1 patient developed Grade 2 CRS and Grade 2 infusion related reactions, 1 patient experienced Grade 2 hypoxia, 1 patient experienced Grade 3 pneumonitis).

Seven deaths (8.6%) reported during the study are displayed in Table 4.f. All of these deaths were considered related to underlying disease progression, and none were considered related to study treatment as assessed by the investigator.

Table 4.f Study TAK-981-1002: On-Study Deaths

TEAE Preferred Term	Number of Patients (%) Total (N = 81)	Dose of TAK-981
Rectal hemorrhage	1 (1.2)	3 mg
Pancreatic carcinoma	1 (1.2)	40 mg
Dehydration (dehydration, ascites, disease progression)	1 (1.2)	60 mg
Small cell lung cancer	1 (1.2)	75 mg
Malignant neoplasm progression (renal cell carcinoma)	1 (1.2)	90 mg
Dyspnea	1 (1.2)	90 mg
Metastatic renal cell carcinoma	1 (1.2)	90 mg

Source: Investigator's Brochure Edition 4, Table 5.l. Data cutoff date: 28 June 2021.
AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE: treatment-emergent adverse event.
AEs graded according to NCI CTCAE Version 5.0.
On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug (AEs with an outcome of death).

As of 30 April 2021, overall 4 patients had DLTs in this study:

- One DLT was observed in the dose level 7 cohort of TAK-981 60 mg BIW in which transient Grade 3 serum ALT and AST elevations with normal bilirubin were observed in a [redacted] patient after the third dose of TAK-981. The ALT and AST elevations resolved within 72 hours, and TAK-981 treatment was resumed at the previous dose level of 40 mg; no liver function test abnormalities were observed following the subsequent 4 doses of TAK-981.
- One DLT was observed in the dose level 8 cohort of TAK-981 90 mg BIW in which Grade 3 recurrent pneumonitis was observed in a [redacted] patient after 4 doses of TAK-981. The patient had a history of Grade 2 pneumonitis during prior treatment with a dual-affinity re-targeting (DART) anti-CTLA-4 and anti-PD-1 antibody. The Grade 3 recurrence of pneumonitis, which was considered an SAE, required treatment with oxygen and steroids; and the patient was discharged after 12 days of hospitalization on a tapering dose of oral steroids and no supplemental oxygen. As a result of this DLT, the Cycle 2 TAK-981 dose 90 mg BIW study medication was withdrawn.
- Two DLTs were observed in the dose level 9 cohort of TAK-981 120 mg BIW.
  - Grade 3 stomatitis was observed in a [redacted] patient after the second dose of TAK-981. The event, which did not require hospitalization, was treated with mouthrinse solution for stomatitis and resolved within 96 hours. The patient received 3 subsequent doses of TAK-981 at 120 mg with no recurrence of the mucositis. From Cycle 2 Day 4, the TAK-981 dose was reduced to 90 mg with no evidence of stomatitis after 6 additional cycles.
  - A Grade 3 cognitive disturbance with Grade 2 lethargy was observed in a [redacted] patient after the first dose of TAK-981. The Grade 3 cognitive disturbance was not

associated with CV instability or abnormal findings in brain magnetic resonance imaging (MRI) and cerebrospinal fluid tests. After 12 days of treatment with IV steroids, symptoms resolved with no sequela. As a result of this DLT, TAK-981 treatment was discontinued.

On 27 May 2021, the 120 mg was determined as the TAK-981 single-agent MTD. TAK-981 90 mg (Days 1, 4, 8, and 11 dosing regimen) regimen was considered as recommended Phase 2 dose (RP2D) and schedule for the subsequent phase 2 portion of the single-agent study. Such dosing regimen will be implemented for 3 cycles of treatment, and subsequent tapering down to TAK-981 90 mg (Days 1 and 8 dosing regimen) will be determined upon sponsor's agreement.

4.2.4.2 Study TAK-981-1501

The study is evaluating the safety, tolerability, and preliminary efficacy of TAK-981 on Days 1 and 8 every 3 weeks. The study is enrolling patients at the starting dose of 10 mg of TAK-981.

In Study TAK-981-1501, as of 28 June 2021, 22 of the 24 patients presented with at least one TEAE. The most common TEAE was pyrexia. Other common TEAEs were diarrhea, chills, dizziness, fatigue, and nausea. There were no reports of CRS as of this data cutoff. Grade ≥3 TEAEs were reported in 9 (37.5%) patients. Two patients experienced Grade ≥3 TEAEs that were considered related to TAK-981 as assessed by the investigator. TAK-981 related Grade ≥3 TEAEs were Grade 4 neutropenia and Grade 3 atrial fibrillation (in patient with ongoing cardiac medical history) in 1 patient each; both the were in 40 mg QW cohort and transient.

Two patients discontinued treatment due TEAEs (1 patient discontinued due to Grade 2 infusion related reaction and 1 patient discontinued due to progression of lymphoma); the events were considered not related to TAK-981 as assessed by the investigator.

More detailed information is provided in the IB.

Overall, TAK-981 has been well tolerated. The majority of the observed AEs were consistent with the patients' underlying cancer disease.

4.3 Rationale for the Proposed Study

Study TAK-981-1002 is the FIH, dose escalation study of TAK-981 in patients with solid tumors or lymphoma followed by a nonrandomized multicohort Phase 2 study in patients with select solid tumor types or NHL indications. TAK-981 is a first-in-class inhibitor of SUMOylation. Nonclinical investigation has demonstrated that TAK-981 promotes production of type I IFNs, inducing an innate immune response capable of bridging to an adaptive antitumor immune response, representing a novel therapeutic strategy for enhancing antitumor immune responses. For the purposes of dose escalation and for evaluating anticancer effects, the study will initially enroll patients with histologically confirmed advanced (loco regionally recurrent, not amenable to curative therapy) or metastatic solid tumors/lymphomas that have no standard therapeutic option with a proven clinical benefit, are intolerant, or patients have refused them.

The study design and patient selection in Phase 1 is adequate to evaluate the initial safety, PK, and pharmacodynamic effects of TAK-981 in patients with cancer.

During Phase 2, patients with any of the 3 specified solid tumor types (NSCLC, cervical cancer, or microsatellite-stable colorectal cancer [MSS-CRC]) or the 3 CD20+ relapsed/refractory NHL indications (FL, DLBCL after CAR T-cell therapy, or DLBCL with no prior cellular therapy) will be enrolled. These tumor types were selected because (1) each represents a significant unmet medical need in the metastatic/refractory setting, (2) there is some evidence of limited clinical response to immune modulators for these indications [43-55], and (3) these indications broadly represent different immune contextures (inflamed, immune excluded, and immune desert). [redacted]

4.3.1 Rationale for the Starting Dose and Schedule

The starting dose of TAK-981 for the study TAK-981-1002 is based upon GLP animal toxicity studies and supported by the estimation of a minimum anticipated biologically effective level (MABEL).

As indicated in ICH S9 [56], the goal of selecting the starting dose in Phase 1 clinical studies for patients with life-threatening malignancies is to identify a dose that is expected to have pharmacologic effects (minimizing exposure to subtherapeutic doses) but is reasonably safe to use. Selection of the safe starting dose for anticancer small molecule inhibitors is traditionally based on either one-tenth of STD10 in rodents or one-sixth the HNSTD in dogs based on body surface area. The STD10 in rats was >60 mg/m^2 (10 mg/kg), and the HNSTD in dogs was 80 mg/m^2 (4 mg/kg) in the 21-day (BIW) GLP-compliant studies. The lower of the 2 values, the STD10 in rats, will be used to inform the starting dose in the FIH Phase 1 study. The starting dose of 10 mg per infusion corresponding with one-tenth the STD10 (10 mg/kg) in the 21-day BIW, study in rats, assuming a human body weight of 70 kg and adjusted for body surface area.

A FIH starting dose selection based on the MABEL is also an approach that can be used for compounds that, like TAK-981, activate the immune system [57]. TAK-981 activates the innate immune system, promoting production of type 1 IFNs. Although there were no elevations in circulating cytokines typically associated with CRS after BIW administration of TAK-981 to rats and dogs (or in an in vitro CRA with human whole blood), there were elevations in body temperature in dogs with daily or weekly dosing (but not BIW dosing), which could be consistent with cytokine-related effects. [redacted]

To assess the effect of TAK-981 on T and NK cell activation, the expression of CD69 activation marker was measured in an ex vivo whole blood assay using flow cytometry. The effect of TAK-981 on DC maturation markers CD40, CD80, and CD86 was measured using flow cytometry. A 2-compartment model of human PK of TAK-981 was projected using a Wajima method [58] based on PK parameters from monkeys administered 0.5 mg/kg TAK-981. The in vitro concentration producing 20% activation (EC_{20}) for the upregulation of CD69 on NK and T cells and CD86, CD80, and CD40 on primary DCs were used to estimate MABEL. CD69 upregulation on NK cells was determined to be the most sensitive marker, yielding the lowest

MABEL corresponding to EC_{20}. Based on this observation in blood from 3 human donors, the median MABEL-derived human-equivalent dose was 3.1 mg for 1-hour IV infusion administration of TAK-981.

As stated above, a starting dose of 10 mg per infusion was calculated following ICH S9 guidelines. Considering the overlapping FIH dose projections using both toxicology based and MABEL approaches, a proposed human starting dose of 3 mg per infusion administered on Days 1, 4, 8, and 11 every 3 weeks is expected to be safe, minimally pharmacologically active, and pose an acceptable risk for monitorable and reversible toxicity in the intended patient population. If clinical safety, PK, and pharmacodynamics are supportive, the protocol schedule can be modified to evaluate a less intensive administration of TAK-981 (eg, on Day 1, or Day 1 and Day 8, or on Day 1, Day 8, and Day 15 in 21-day cycles) without requiring a protocol amendment.

4.3.2 Rationale for [redacted] Skin, and Blood Tissue Sample Collection

[redacted] skin, and/or blood tissues will be collected to determine target engagement and to assess pharmacodynamic biomarkers supportive of TAK-981's mechanism of action and biologically effective dose (BED) determination (Section 8.2.3).

4.3.2.1 [redacted]

[redacted]

4.3.2.2 Skin Biopsies

Skin punch biopsies will be collected to determine target engagement and SUMO2/3 inhibition in a surrogate tissue.

4.3.2.3 Blood

Blood samples will be collected to demonstrate target engagement, SUMO pathway inhibition, [redacted]

4.4 Potential Risks and Benefits

TAK-981 is currently being evaluated in this ongoing FIH Phase 1/2 study in patients with advanced or refractory solid tumors or lymphomas (Study TAK-981-1002) and 1 ongoing Phase 1b/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). Preliminary safety information in described in Section 4.2.4.

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.

4.4.1 Potential Effects Based on Nonclinical Studies

Potential risks based on a non-GLP repeat dose nonclinical toxicology study with daily dosing in rats; GLP repeat dose, nonclinical toxicology studies with once or BIW dosing in rats and dogs; a single dose safety pharmacology study in dogs; a PK study in cynomolgus macaques; an in vitro assessment of mutagenicity and an in vivo assessment of genotoxicity in rats; and a non-GLP in vitro CRA in human PBMCs, are summarized below. Further details for TAK-981 administration, safety events, and management can be found in Section 8.1, Section 8.6, and the Guidance for Investigator section of the IB.

4.4.1.1 Lymphoid and Hematopoietic Effects

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

Lymphopenia may predispose patients to certain forms of infection that were not observed in the GLP-compliant toxicology studies. Prolonged lymphopenia and CD4 counts below 200/µL have been associated with opportunistic infections. Prophylaxis for pneumocystis pneumonia or herpes zoster is not required; however, in cases of prolonged lymphopenia, or in patients with a previous history of shingles, it might be initiated per SOC.

As of the data cutoff for this report in the ongoing clinical studies, transient decrease lymphocyte count (3.7%) related to TAK-981 has been reported. Opportunistic infections have not been reported to date; however, herpesvirus reactions have been observed (1.5% related to TAK-981) but were self-limited, resolving within 14 days.

In this study, absolute lymphocyte counts will be monitored, and subpopulations will be assessed regularly, especially CD4 and CD8 counts. A prolonged CD4 count below 200/µL (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] ≥Grade 3) is the strongest predictor for opportunistic infections. The initiation of *Pneumocystis jirovecii* pneumonia prophylaxis and herpes virus prophylaxis will be considered at the discretion of the investigator.

4.4.1.2 Effects in Renal Pelvis

TAK-981–related effects were observed in the kidney (renal pelvis) in dogs (following repeat daily-to-BIW dosing) and consisted of reversible inflammation and arteriolar fibrinoid necrosis localized to the renal pelvis. There were no effects in the renal cortex or medulla; there were no repercussions on kidney function or conventional urinary test parameters. After a 10-day nondosing period, arteriolar fibrinoid necrosis was completely reversed and inflammation was partially reversed. Lesions in the renal pelvis could be associated with alterations in urinary sediment and susceptibility to urinary infections in the clinic, although these potential effects were not observed in dogs.

Inflammation in the renal pelvis suggests a local effect of concentrated drug or a metabolite. Patients will be asked to maintain adequate hydration (1.5 to 2 L/day) 48 hours before initiating therapy, and IV fluid administration on Cycle 1, Day 1 (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.

4.4.1.3 IRRs and Potential for CRS

The mechanism of action of TAK-981 involves type 1 IFN signaling and for this reason 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 while no increases in cytokines related to CRS including interleukins IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IFNγ, G-CSF, or TNFα were 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 4.2.3).

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 infusion reactions/CRS, during dose escalation, patients will be hospitalized overnight for the first infusion of TAK-981. For the remaining infusions (and only in case no AE is being observed), the patient will be observed a minimum of 4 hours after end of infusion 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, patient enrollment is staggered between the first and second patients 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 the Day 4 visit without clinically significant acute toxicities (Section 6.1).

4.4.1.4 Injection Site Reactions

The local irritancy potential of TAK-981 was evaluated at the IV administration site in the GLP-compliant repeat-dose toxicity studies in rats and dogs. Effects at the injection site, including potentiation of procedure-related subcutaneous hemorrhage, inflammation, and necrosis, were observed in rats only. The shorter needle length and frequent movement of conscious rats likely resulted in extravasation. Of note, TAK-981 is a solution with low pH that should be diluted, as defined in the pharmacy manual.

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).

4.4.1.5 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 not known at this time. 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. TAK-981–related reproductive findings were not observed in the studies with BIW dosing and in the dog study 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, inflammation in the prostate gland, and (at ≥5 mg/kg) partially reversible acinar cell trophy in the male mammary gland. 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.

Therefore, female patients and female partners of male patients participating in this study should avoid becoming pregnant. Nonsterilized female patients of reproductive age group 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 6 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 patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 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 patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

4.4.1.6 Genotoxicity

TAK-981 was not mutagenic in an in vitro bacterial mutagenesis Ames assay. However, in an in vivo rat bone marrow micronucleus assay, TAK-981 increased induction of micronuclei and was therefore considered to be positive for in vivo genotoxicity at ≥5 mg/kg. It was not determined whether TAK-981 induces clastogenic or aneugenic genotoxicity. In compliance with ICH S9 guidance (ich.org/products/guidelines/safety/article/safety-guidelines.html), carcinogenicity assessment is not planned.

The potential effects listed above are based on toxicology findings in the nonclinical studies with TAK-981; they 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.

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, the Safety Monitoring Committee (SMC) will continuously monitor patients in dose escalation and cancer treatment expansions; the Independent Data Monitoring Committee (IDMC) will monitor patients in the Phase 2 study.

4.4.2 COVID-19 Pandemic

The 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.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

Phase 1:

- To determine the safety and tolerability of TAK-981 as a single agent in patients with advanced or metastatic solid tumors and lymphomas.
- To establish the RP2D of TAK-981.

Phase 2:

- To evaluate preliminary efficacy of TAK-981 in patients with select solid tumors or relapsed/refractory CD20+ NHL indications.

5.1.2 Secondary Objectives

Phase 1:

- To assess the preliminary antitumor activity of TAK-981.
- To assess target engagement of TAK-981 (SUMO-TAK-981 adduct formation) and SUMOylation pathway inhibition in skin and peripheral blood cells.
- To characterize the PK profile of TAK-981.

Phase 2:

- To evaluate the efficacy of TAK-981 in select solid tumor and CD20+ NHL indications as measured by time to response (TTR), DOR, disease control rate (DCR), time to progression (TTP), and PFS.
- To evaluate OS.
- To evaluate the safety and tolerability of TAK-981.
- To collect plasma concentration-time data for TAK-981.

5.1.3 Exploratory Objectives

[redacted]

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

Phase 1:

- 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 American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS [1].
- DLTs within the first 21 days of treatment in Cycle 1.

Phase 2:

- ORR (CR + PR) as defined by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) criteria for solid tumors or Lugano classification for lymphomas.

5.2.2 Secondary Endpoints

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

Phase 1:

- ORR, DCR, DOR, TTP, TTR, and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or 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 [1].
- DCR, DOR, TTR, TTP, and PFS as assessed by the investigator according to RECIST v1.1 criteria for solid tumors or Lugano classification for lymphomas and OS.

5.2.3 Exploratory Endpoints

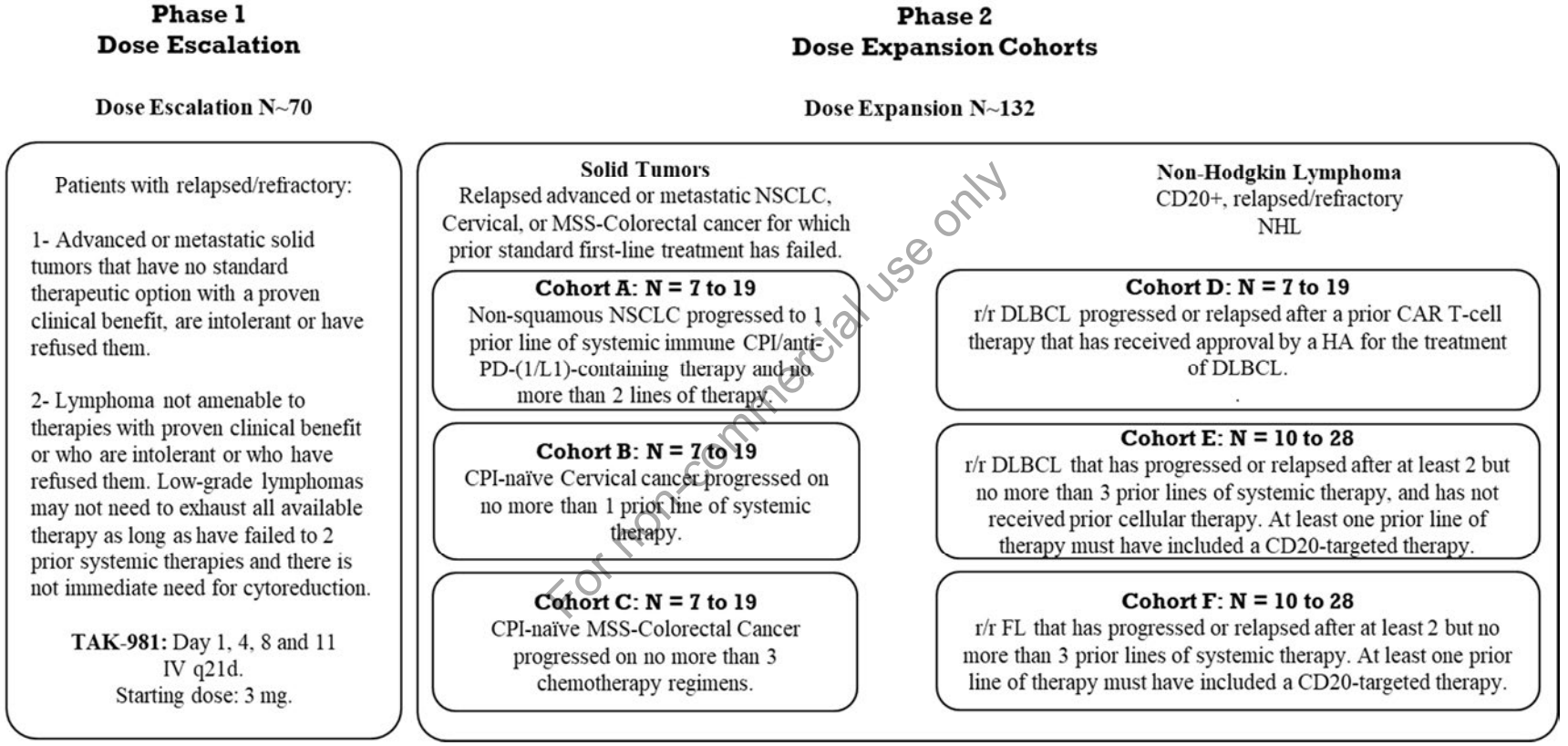
[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a Phase 1/2, open-label, dose-escalation and dose expansion study designed to evaluate safety, tolerability, preliminary efficacy, and PK of single agent TAK-981 in adult patients with advanced or metastatic solid tumors or lymphomas (Figure 6.a).

Figure 6.a TAK-981-1002 Study Design

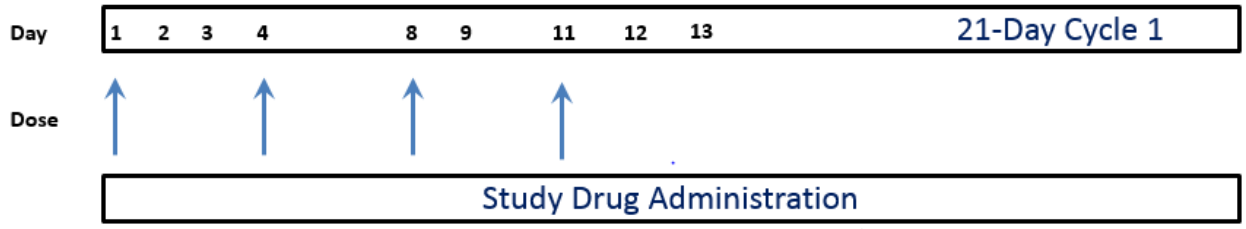


CAR: chimeric antigen receptor; CPI: checkpoint inhibitor; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HA: health authority; IV: intravenous administration; MSS: microsatellite-stable; NHL: non-Hodgkin lymphoma; NSCLC: non–small cell lung cancer; r/r: relapsed/refractory; PD-(1/L1): programmed cell death protein 1/programmed death ligand 1; q21d: every 21 days.

6.1.1 Phase 1 Dose Escalation

Patients will be treated in cohorts with increasing doses of TAK-981, administered as a 1-hour IV infusion on Days 1, 4, 8, and 11 of a 21-day cycle until a discontinuation criterion is met. The overall dosing regimen is displayed in Figure 6.b.

Figure 6.b TAK-981 Dosing Regimen



The study will begin with a dose escalation. Dose escalation intervals progress from 3 mg to 160 mg (with a provision of 1 mg at dose level 1). The upper dose level corresponds approximately to the human equivalent dose of the MTD in dogs. Patient enrollment will be staggered between the first and second patients 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 the Day 4 visit 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 may not be required if there are no clinically significant safety findings suggestive of infusion reaction or CRS.

Dose escalation of TAK-981 will be cohort-based with an adaptive design using Bayesian logistic regression modeling (BLRM) (see Appendix G for details). Approximately 70 patients will be enrolled until the RP2D of TAK-981 is identified. Single agent RP2D could be based either on the MTD based on the observation of DLTs (Section 8.2.1) or a BED that is ≤MTD.

A minimum of 3 patients will be enrolled in the starting dose cohort. Dose escalation and cohort expansion decisions are reviewed and approved by the SMC, composed of the sponsor clinician and the investigators, which may decide that a fourth patient can be recruited to the same cohort before the first 3 patients complete the DLT assessment period. While the first 3 evaluable patients will be used to determine dose expansion, if the fourth patient experiences a DLT, their respective AE(s) will be taken into consideration regarding cohort determination, during the end of cohort meeting. The rationale for such an addition is to have an extra patient in the cohort should 1 of the 3 earlier patients be unevaluable, or if a patient within the cohort experiences a DLT, which would require cohort expansion to 6 patients. From dose level 2 onwards, an adaptive BLRM guided by the Escalation with Overdose Control principle will be used in successive escalation cohorts (Section 8.2.2).

Single agent RP2D will be based either on the MTD determined by the BLRM (Section 8.2.1) or a BED that is ≤ MTD. The BED of TAK-981 is defined as the dose at which there is evidence of pharmacodynamic effects including the presence of SUMO-TAK-981 adducts and inhibition of

SUMO2/3 conjugates, [redacted].

If clinical safety, PK, and pharmacodynamics are supportive, the protocol schedule can be modified to evaluate a less intensive administration of TAK-981 (eg, Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 in 21-day cycles). Once the RP2D is defined, patients on schedules other than RP2D may be transitioned to the RP2D schedule upon discussion and agreement between the investigator and sponsor.

Circumstances that may warrant enrollment hold include the determination of an overall excess of toxicity:

1. The study will be stopped if the cumulative frequency of DLTs or DLT-like AEs (those AEs meeting the criteria of DLT outside of the DLT-evaluation period) is greater than 40% at any point during the trial.
2. For the 70 patients expected to be treated during the dose-escalation, the study will be stopped if 3 fatal AEs related to TAK-981 occur, at least 2 of them within the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (excluding deaths that happen during the exploration of a dose level that is above the MTD). Additionally, if 2 fatal AEs related to TAK-981 within the same System Organ Class occur during the treatment of the first 12 patients, enrollment will be also halted.

The stop will result in an immediate halt in enrollment and may also necessitate the halting of treatment of ongoing patients, depending on the nature and severity of the safety risk. A final decision to terminate the study or a protocol amendment will be made only after a full review of the safety data by the SMC and safety management team.

6.1.2 Phase 2 Expansion in Select Cancer Indications

Once the RP2D is defined, the study will explore the efficacy and safety of TAK-981 in patients with select cancers. The following cohorts will be enrolled (Figure 6.a):

- Cohort A: Nonsquamous NSCLC.
- Cohort B: Cervical cancer.
- Cohort C: MSS-CRC.
- Cohort D: Relapsed/refractory DLBCL progressed or relapsed after CAR T-cell therapy.
- Cohort E: Relapsed/refractory DLBCL that have not received prior cellular therapy.
- Cohort F: Relapsed/refractory FL.

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 (as defined in Section 13.3) have been enrolled and had the potential to have at least 1 posttreatment scan (ie, after the first disease assessment, 2 months from C1D1). 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 clinical benefit has been observed for patients in the cohort (eg, the majority of patients have recorded stable disease (SD) at Week 8 and per investigator assessment are benefiting from treatment), then enrollment into stage 2 may be allowed for this cohort with agreement from participating investigators. 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 take place when all ongoing patients have had the opportunity complete the 6 months disease assessment.

On 27 May 2021, a regimen of 90 mg TAK-981 with dosing on Days 1, 4, 8, and 11 was considered to be theRP2D and schedule for the subsequent phase 2 portion of the single-agent study. This dosing regimen will be implemented for 3 cycles of treatment, and subsequent tapering down to 90 mg TAK-981 (Days 1 and 8 dosing regimen) will be determined on the sponsor's agreement.

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.

6.2 Number of Patients

Up to approximately 202 patients will be enrolled in the study.

6.2.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

During the dose escalation phase, approximately 70 DLT-evaluable patients will be enrolled at approximately 7 to 12 study centers in the US and Canada.

During Phase 2, up to approximately 19 to 28 patients will be enrolled in each of the solid tumor or the CD20+ relapsed/refractory NHL cohorts.

6.3 Patient Replacement

In Phase 1 part of the study, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT may be replaced. Patients in Phase 2 will not be replaced.

6.4 Duration of Study

6.4.1 Duration of an Individual Patient's Study Participation

6.4.1.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

Patients may receive TAK-981 up to 1 year. Patients with demonstrated clinical benefit can continue treatment beyond this point if approved by the sponsor. These patients can continue receiving treatment in this study or in any of the poststudy access modalities described in Section 6.4.5. Patients may discontinue treatment if they meet any of the discontinuation criteria in Section 8.2.4.1.3.

All patients will attend an end-of-treatment (EOT) visit 30 days (+10 days) after receiving their last dose of study drug 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 in Phase 1 who discontinue study treatment for reasons other than progressive disease in dose escalation will continue PFS follow-up every 12 (±1) weeks from the EOT visit for up to 12 months or until a discontinuation criterion is met (Section 9.7). Patients in Phase 2 who discontinue or complete treatment will be followed for survival every 12 (±1) weeks from the EOT visit for up to 12 months after the last patient in the cohort discontinues or completes treatment, or until loss of follow-up, consent withdrawal, death, study termination, or until >70% of patients in the cohort have progressed, whichever occurs first.

6.4.2 End of Study/Study Completion Definition and Planned Reporting

6.4.2.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts Primary Completion/Study Completion

The primary analyses for the primary endpoint will be conducted after all patients enrolled in the study have had the opportunity to complete 9 cycles of treatment with TAK-981. 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 6.4.5). The estimated time frame for study completion is up to 48 months.

6.4.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Phase 1		
Primary Endpoint:		
Frequency and severity of TEAEs overall and per dose level	Standard safety assessments	Up to 48 months
Number of patients with DLTs per dose level	Standard safety assessments	Up to 48 months
Number/percentage of patients with clinically significant laboratory values	Standard safety assessments	Up to 48 months
Secondary Endpoints:		
PK parameters after the first dose of TAK-981 on C1D1 and C1D8 (data permitting): C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2z}$, CL, V_{ss}	Standard PK parameters to allow determination of PK profile	Up to 48 months
Response assessments based on RECIST v1.1 for solid tumors or Lugano classification for lymphomas: ORR, DOR, DCR, TTR, TTP, PFS	Standard efficacy assessments	Up to 48 months
TAK-981-SUMO adduct formation and SUMO pathway inhibition	TAK-981-SUMO adduct formation and SUMO pathway inhibition on skin tissues/blood	Up to 48 months
Phase 2		
Primary Endpoint:		
ORR (CR + PR) as defined by the investigator according to RECIST v1.1 for solid tumors or Lugano classification for lymphomas	Standard efficacy assessments	Up to 48 months
Secondary Endpoints:		
Plasma TAK-981 concentration-time profile	Standard PK parameters to allow determination of PK profile	Up to 48 months
Frequency and severity of TEAEs	Standard safety assessments	Up to 48 months
Response assessments based on RECIST v1.1 for solid tumors or Lugano classification for lymphomas:		
DOR, DCR, TTR, TTP, PFS	Standard efficacy assessments	Up to 48 months
OS	Standard efficacy assessments	Up to 48 months

AUC_{last}: area under the plasma/blood/serum concentration-time curve from time 0 to the last measurable concentration; AUC_{∞}: area under the plasma/blood/serum 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; CR: complete response; DCR: disease control rate; DLT, dose-limiting toxicity; DOR: duration of response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK, pharmacokinetic; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors Version 1.1; SUMO, small ubiquitin-like modifier; $t_{1/2z}$: terminal disposition phase half-life; TEAE: treatment-emergent adverse event; t_{max}: time of first occurrence of maximum observed plasma concentration; TTP: time to progression; TTR: time to response; V_{ss}: volume of distribution at steady state after intravenous administration.

6.4.4 Total Study Duration

Phase 1 and Phase 2: It is anticipated that this study will last for approximately up to 48 months.

6.4.5 Poststudy Access

6.4.5.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

Participants 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 may continue to receive TAK-981 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 TAK-981. 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 for participants will be terminated for those individuals who no longer benefit from TAK-981 (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 becomes available either commercially or via another 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

Male or female patients aged 18 years or older with histologically or cytologically confirmed solid tumors or relapsed/refractory hematologic malignancies.

7.1 Inclusion Criteria

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

1. Adult male or female patients ≥18 years old.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
3. Patient population for Phase 1 dose escalation:
   a. Have a histologically or cytologically confirmed advanced (local regionally recurrent not amenable to curative therapy) or metastatic solid tumors who have no standard therapeutic option with a proven clinical benefit, are intolerant, or have refused them.

      OR

   b. Have a relapsed/refractory lymphoma not amenable to therapies with proven clinical benefit or who are intolerant or who refuse them. Patients with low-grade lymphomas such as FL, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, and marginal zone

lymphomas may not need to exhaust all available therapy. These patients can be enrolled after failure of at least 2 prior systemic therapies, provided that there is not an immediate need for cytoreduction. In these cases, patients who need immediate therapy for tumor bulk are not eligible for this trial.

4. Patient population for Phase 2 dose expansion cohorts:

   Have a histologically or cytologically documented, advanced (metastatic and/or unresectable) cancer as listed below, that is incurable and for which prior standard first-line treatment has failed:

   Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line SOC treatment unless such treatments were completed less than 12 months before the current tumor recurrence.

   a. Nonsquamous NSCLC that has progressed to 1 prior systemic immune CPI/anti-PD-(1/L1)-containing therapy and no more than 2 lines of therapy. Patients must have not shown evidence of tumor progression during the first 5 months of treatment with first-line CPI/anti-PD-(1/L1)-containing therapy (cohort A).

      Note: Patients with known driver mutations/genomic aberrations (eg, *EGFR*, B-Raf proto-oncogene mutation V600E [*BRAF* V600E], and ROS proto-oncogene 1 [ROS1] sensitizing mutations, neurotrophic receptor tyrosine kinase [*NRTK*] gene fusions, and anaplastic lymphoma kinase [*ALK*] rearrangements) must have also shown progressive disease after treatment with a commercially available targeted therapy.

   b. CPI-naïve cervical cancer (squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix) patients who have received no more than 1 prior systemic line of therapy for recurrent or Stage IVB cervical cancer (cohort B).

      Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric-type adenocarcinoma, clear-cell carcinoma, and mesonephric carcinoma. Histologic confirmation of the original primary tumor is required via pathology report.

      Note: First-line treatment must have consisted of platinum-containing doublet. Chemotherapy administered concurrently with primary radiation (eg, weekly cisplatin) is not counted as a systemic chemotherapy regimen.

   c. CPI-naïve MSS-CRC patients who have progressed on no more than 3 chemotherapy regimens (cohort C).

      Note: Patients must have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens if indicated.

   d. Relapsed/refractory DLBCL progressed or relapsed after prior CAR T-cell therapy that has received approval by a health authority for the treatment of DLBCL (cohort D).

e. Relapsed/refractory 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 E).

f. Relapsed/refractory 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 F).

5. In Phase 2 only, have at least 1 radiologically measurable lesion based on RECIST v1.1 for patients with solid tumors or Lugano criteria for lymphoma. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: In Phase 2 stage 1, have an additional lesion for pretreatment and on-treatment biopsy.

6. In Phase 2 stage 1, willing to consent to mandatory pretreatment and on-treatment tumor biopsy.

   Note: For fresh tumor biopsies, the lesion must be accessible for a biopsy procedure as assessed by the investigator.

7. Is willing to provide archival tumor tissue sample, if available.

8. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:

   a. Absolute neutrophil count (ANC) ≥1.0 × 109/L, hemoglobin ≥85 g/L (RBC transfusion allowed ≥14 days before assessment), and platelet count ≥75.0 × 109/L (platelet count ≥50.0 × 109/L is allowed for patients with lymphoma if it is clearly due to marrow involvement with no evidence of myelodysplastic syndrome or hypoplastic bone marrow, if found).

   b. Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN); or total bilirubin <3.0 times the ULN with direct bilirubin within normal range in patients with well-documented Gilbert's syndrome.

   c. Serum ALT or AST ≤3.0 times the ULN (<5 times the ULN if liver enzyme elevations are due to liver metastases).

   d. Estimated creatinine clearance using the Cockcroft-Gault formula ≥45 mL/minute.

9. Recovered to Grade 1 or baseline or established as sequelae from all toxic effects of previous therapy (except alopecia, neuropathy, or autoimmune endocrinopathies with stable endocrine replacement therapy, or bone marrow parameters [any of Grade 1/2 permitted if directly related to bone marrow involvement]).

10. Consented to undergo serial skin punch biopsies (dose escalation only).

11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

12. Suitable venous access for safe drug administration and the study-required PK and pharmacodynamic sampling.
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:
    a. Postmenopausal for at least 1 year before the screening visit, or
    b. Surgically sterile, or
    c. 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 6 months after the last dose of study drug, or
    d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], 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 post vasectomy) must agree to 1 of the following:
    a. Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

7.2 Exclusion Criteria

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

1. Phase 1 dose escalation and Phase 2 cancer treatment expansion cohorts:
    a. Have received treatment with systemic anticancer treatments or investigational products within 14 days before the first dose of study drug or 5 half-lives, whichever is shorter.

    Note: Low-dose steroids (oral prednisone or equivalent ≤20 mg per day), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed.

    b. Have received extended field radiotherapy ≤4 weeks before the start of treatment (≤2 weeks for limited field radiation for palliation), and who has not recovered to grade 1 or baseline from related side effects of such therapy (except for alopecia).

2. Have a history of uncontrolled brain metastasis. Patients with brain metastases are allowed if they are previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery and the patients are receiving a corticosteroid dose ≤10 mg/day of prednisone equivalent at the time of receiving the first dose of TAK-981. For asymptomatic patients, screening brain imaging is not required.
3. Patient is receiving any live vaccine (eg, varicella, pneumococcus) within 4 weeks of initiation of study treatment.
4. History of any of the following ≤6 months before first dose: congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, unstable symptomatic ischemic heart disease, severe noncompensated hypertension despite appropriate medical therapy, 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.
5. Baseline prolongation of the QT interval with Fridericia correction method (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
6. Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or has compromised ability to provide written informed consent.
7. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
8. History of autoimmune disease requiring systemic immunosuppressive therapy with daily doses of prednisone >10 mg/day or equivalent doses, or any other form of immunosuppressive therapy. Hormone therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered an excluded form of systemic treatment of an autoimmune disease.
9. History of immune-related AEs related to treatment with immune checkpoint inhibitors that required treatment discontinuation.
10. History of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
11. Has evidence of active, noninfectious pneumonitis.
12. Have a significant active infection.
13. Known history of HIV infection or any other relevant congenital or acquired immunodeficiency.
14. Known hepatitis B virus surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.

15. Receiving or requiring the continued use of medications that are known to be strong or moderate inhibitors and inducers of CYP3A4/5 (Appendix E) or are strong P-gp inhibitors (Appendix F). To participate in this study, patients should discontinue use of such agents for at least 2 weeks (1 week for CYP3A4/5 and P-gp inhibitors) before receiving a dose of TAK-981.
16. Patient requires the use of drugs known to prolong QTc interval (during Phase 1 only) (Appendix H).
17. History of allogeneic tissue or solid organ transplant.
18. 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.
19. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

8.0 STUDY DRUG

Patients enrolled in the study will receive TAK-981 as a single agent.

8.1 Study Drug Administration

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

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

TAK-981 will be administered as 60 (±10) minute IV infusion. In case infusion reactions are observed, the length of the infusion can be extended up to 2 hours for all patients without needing a protocol amendment.

TAK-981 administration should occur in an area with resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Patients' vital signs must be monitored before, during the, and at the end of administration of TAK-981. Treatment must be stopped if the patient experiences symptoms compatible with an infusion reaction of Grade 2 or greater. The management of infusion reactions and CRS is detailed in Sections 8.6.6 and 8.6.7, respectively.

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 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

In Phase 1 dose escalation and Phase 2 cancer treatment expansion, each 21-day treatment cycle will consist of a single dose TAK-981 administration on Days 1, 4, 8, and 11. Evaluation of alternative TAK-981 dosing schedules (eg, Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 in 21-day cycles) may be permissible only after discussions between the sponsor and the investigators.

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. On C1D1 in Phase 1, patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours before collection of the predose ECGs until after collection of the 1-hour postinfusion ECGs. A low calorie and low sodium light meal is permitted immediately after the 1-hour postinfusion ECG has been collected. No diet restriction will be required during Phase 2.

During Phase 1, for the first infusion (C1D1) of TAK-981 during dose escalation every patient needs to be hospitalized for drug administration and overnight observation (a minimum of 18 hours after the end of infusion). The patient can be discharged from overnight observation only if there are no signs and symptoms of acute toxicity like fever or significant changes in blood pressure and/or heart rate. Prophylaxis for IRRs is not recommended for the first dose of TAK-981. Hospitalization is not required if expansion after the first 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 no infusion reaction is observed in C1D1, subsequent infusions (C1D4 infusion onwards) can be administered in an outpatient basis.

During Phase 1 C1D1 administration, vital signs (blood pressure, heart rate, and temperature) should be monitored for at least 6 hours after infusion and again before discharging the patient or at any time if the patient complains of symptoms. If an AE is observed, extended monitoring of vital signs can be added as medically indicated. Outside C1D1, vital signs need to be monitored as stated above and up to 4 hours after the end of the infusion. From Cycle 2 onwards, if no infusion reaction is observed in the first cycle, the patient can be discharged from the site per investigator discretion.

During Phase 2 C1D1, vital signs should be monitored up to 4 hours after the end of the infusion. Outside C1D1, vitals will be monitored immediately before the start of infusion and after the end of infusion, and patients will be discharged per investigator discretion.

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 (see Section 8.4). For patients in the DLT-evaluation period (Cycle 1), rescheduling is allowed for a maximum of 1 dose. At least 72 hours should elapse between consecutive doses of TAK-981.

8.2.1 Definitions of DLT for Dose Escalation

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 [1]. 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 with TAK-981:

1. Any Grade 5 AE.
2. Nonfebrile Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) lasting more than 7 consecutive days. If myeloid growth factors are used, the event will be considered as DLT irrespective of the duration.
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 more than 7 consecutive days. A platelet count $<10 \times 10^9$/L at any time is a DLT.
5. Grade 3 thrombocytopenia lasting longer than 14 days or accompanied by Grade 2 bleeding or requiring transfusion.
6. Delay in the initiation of Cycle 2 by more than 14 days due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
7. Grade ≥3 nonhematologic toxicity with the following exceptions:
   - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs within 1 week.
   - Grade 3 fatigue lasting fewer than 7 days.
   - 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.
   - Grade 3 CRS that resolves to ≤Grade 1 in less than 7 days without end-organ damage.
   - Asymptomatic laboratory changes (other than renal and hepatic laboratory values) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
   - Grade 3 elevation in ALT, AST, and/or alkaline phosphatase that resolves to Grade ≤2 or baseline with supportive care within 7 days and is not associated with other clinically relevant consequences.
   - Grade 3 nausea and/or emesis that can be controlled to <Grade 3 in ≤3 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 diarrhea that can be controlled to <Grade 3 in ≤3 days with appropriate treatment.
- Grade 3 rash lasting ≤7 days after treatment that includes topical steroid treatment, oral antihistamines, and pulse oral steroids (if necessary).

8. Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug and dose-limiting.

AEs meeting the DLT definition may occur at any point during treatment. Primarily, only DLTs occurring during Cycle 1 of treatment will influence decisions regarding dose escalation; however, BLRM also will take into consideration DLTs occurring at later treatment cycles. For the selection of RP2D, the total frequency of DLTs and DLT-like AEs should be <33%. If a patient in the dose escalation phase does not receive all planned doses for Cycle 1 for reasons other than a DLT, that patient will be replaced.

8.2.2 Dose Escalation Rules

Dose escalation of TAK-981 will be cohort-based. Initially, 3 patients will be enrolled at the starting dose level. When Cycle 1 safety data are available from the first 3 evaluable patients in the current cohort, the final decision on next dose level will be taken by the SMC. The SMC may decide that a fourth patient can be recruited before the first 3 patients complete the DLT assessment period. The rationale for such an addition is to have an extra patient in the cohort should 1 of the 3 earlier patients be 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 has a Cycle 1 DLT, the starting dose will be considered not tolerated and the dose will be de-escalated to 1 mg. If none of the 3 additional patients has 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.

While the first 3 evaluable patients will be used to determine dose expansion, if the fourth patient experiences a DLT, their respective AE(s) will be taken into consideration regarding cohort determination, during the end of cohort meeting.

Starting from the second dose level, the BLRM with overdose control along with consideration of other safety, clinical, PK, and pharmacodynamic data, will be used for all subsequent dose recommendations. Starting from the second dose level, the size of the cohort will be approximately 3 subjects. 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 DLT, exposure, or pharmacodynamics.

Before initiating the dosing of the next cohort, when Cycle 1 safety data are available for all patients in the current cohort, an end of cohort meeting will be held. The SMC will review the Cycle 1 safety data of all treated patients, the available PK and pharmacodynamic information, and make decisions regarding dose escalation. Any decision to modify the dose escalation scheme or infusion schedule (with the exception of de-escalation, escalation to intermediate doses, or reduction in the administration frequency [eg, Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15]) will be introduced as a protocol amendment and will need to be approved by the institutional review boards (IRBs) before being implemented. All decisions will be documented in writing.

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 Appendix G). Escalation will 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 and the posterior probability of the next recommended dose 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 SMC may decide to stop dose escalation without identifying MTD based solely on pharmacodynamic markers. In this case BED will be declared (Section 8.2.3). 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.

Patients not receiving all doses of TAK-981 in Cycle 1 for reasons other than DLTs will be replaced within the cohort.

Table 8.a Planned Dose Levels

Dose Level	Dose (Unit) [a]
For Cancer Treatment Cohorts	
-1	1 mg
1	3 mg
2	6 mg
3	10 mg
4	15 mg
5	25 mg
6	40 mg
7	60 mg
8	90 mg
9	120 mg
10	160 mg

[a] Dose levels indicate the maximum dose escalation per step. Intermediate dose levels can be used based on clinical observations.

8.2.3 Definition of BED

The BED of TAK-981 is defined as the dose at which there is evidence of pharmacodynamic effects including the presence of SUMO-TAK-981 adducts and inhibition of SUMO2/3 conjugates, [redacted] BED can be defined retrospectively once MTD is reached and it can be below MTD or coincide with it.

8.2.4 Dose Modification Guidelines for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

Dose modification guidelines for toxicities for patients enrolled in dose escalation or cancer treatment expansions 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).

8.2.4.1.1 Intrapatient Dose Escalation

Patients who have tolerated treatment with TAK-981 well at the initially assigned dose may be allowed to increase their doses of TAK-981 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.

8.2.4.1.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with TAK-981 will use a cycle length of 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 in patients with lymphoma if no change in the baseline platelet level from the screening visit and it is clearly due to marrow involvement).

Before starting a new treatment cycle, TAK-981–related AEs or laboratory abnormalities must have returned to ≤Grade 1/baseline (other than those stated above). If the patient fails to meet the above-cited criteria 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, this will be considered a DLT (if considered as possibly related and happens in Cycle 1) and 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. If clinical benefit for the individual patient is confirmed, recovery period can be extended or retreatment at the same or reduced dose can be started without complete recovery. TAK-981 dosing may be continued at the previously established safe dose level or below.

8.2.4.1.3 Criteria for Dose Interruption, Dose Reduction, and Discontinuation

All toxicities that occur during the study will be actively managed following the SOC unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-981 may continue study treatment with the same dose, may have TAK-981 treatment held or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs should resume study drug treatment after resolution of the AE to Grade ≤1 or baseline (or Grade 2 for some specified hematological AEs as shown in Table 8.c), at the next lower dose level.

Dosing of TAK-981 should be interrupted or reduced according to the dose modification recommendations listed in Table 8.b for nonhematologic toxicity and Table 8.c for hematologic toxicities. When the dose of TAK-981 is withheld based on the listed criteria, clinical and laboratory reevaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed until the toxicity resolves to the Grade specified in Table 8.b and Table 8.c. 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 cannot be administered 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 the schedule of events (SOE) (Appendix A).

If initial dose adjustment does not provide sufficient relief, the dose of TAK-981 can be further reduced by another dose level if the treating physician considers that the patient is receiving benefit. 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. A patient can receive up to 2 dose level reductions of TAK-981 due to AEs but further reductions are not permitted (the patient should discontinue study drug in this case).

In dose escalation, the dose of TAK-981 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

Table 8.b 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, at the previous safe 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. Note: Permanently discontinue treatment if Grade ≤3 QTcF prolongation occurs.
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; QTcF: QT interval with Fridericia correction method.

For specific instructions in case of CRS, refer to Table 8.d.

Table 8.c Dose Adjustments for Hematologic Toxicities

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)	Continue TAK-981 at the same dose level.
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)	Withhold dose until resolved to ≤Grade 1 or baseline, then:
Grade 3 (PLT <50.0 - 25.0 × 10^9 cells/L) without bleeding	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.
PLT <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 the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor, then resume treatment at the previous safe lower dose level (ie, reduce by 1 dose level).

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

Criteria for Discontinuation of TAK-981

In dose escalation, TAK-981 should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that retreatment of the patient could be dangerous. For Grade 4, life-threatening nonhematologic TEAEs, permanently withdraw the patient from the study.

If more than 2 dose reductions are required, or if the next cycle of TAK-981 is delayed for >14 days because of TAK-981–related toxicities, then the patient should have study treatment discontinued unless the investigator considers that the patient will receive benefit from continuing in the study. If treatment discontinuation is determined, the EOT visit should be completed within 30 (+10) days of the last administration of TAK-981 and before the start of subsequent anticancer therapy.

8.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- 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. Patients in dose escalation or cancer treatment expansions can resume treatment with TAK-981 approximately 2 weeks or 5 times the half-life (whichever is shorter) after discontinuing the use of these strong and moderate inhibitors and inducers of CYP3A4/5.

8.3.1 Excluded Concomitant Medications and Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

- 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 (<96 hours) for exacerbations of respiratory tract disorders or for acute control of emerging tumor pain.
- Strong inhibitors of P-gp (see list in Appendix F).
- In Phase 1, initiation of prophylactic use of myeloid growth factors (eg, G-CSF) are not allowed in the first cycle before confirmation of DLT but may be administered to manage patients who experience Grade 4 and/or febrile neutropenia if clinically indicated in accordance with American Society of Clinical Oncology guidelines and/or institutional practices. For the first episode of neutropenia, dose reduction is preferred.
- Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin, but initiation of new erythropoietin therapy is not allowed during the first cycle.
- 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 progressive disease is ruled out) or standard or investigational agents for treatment of cancer.
- Drugs known to prolong QTc interval, during Phase 1 only (see list in Appendix H).
- Because the safety of immunization with live viral vaccines following TAK-981 therapy has not been studied, vaccination with live virus vaccines is prohibited while the patient is being treated on study.

8.4 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:

- 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 P-gp 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 before treatment initiation. COVID-19 vaccination should follow local guidances and regulations. Ideally, patients will have completed vaccination before treatment initiation. For patients enrolled in Phase 1, vaccination during Cycle 1 is not permitted because 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. COVID-19 vaccine should be captured as a concomitant medication.

Additional concomitant medications and procedures are permitted during the study to prevent and actively manage AEs. Treatment of AEs with prohibited concomitant medications (except anticancer treatments) is allowed per the investigator's judgment. In this situation, treatment with TAK-981 must be interrupted. Treatment with TAK-981 may be resumed, if the patients meets criteria for resuming treatment with TAK-981, once treatment with the prohibited medication is stopped and a washout period (7 days or 5 half-lives whichever is shorter) is completed. This situation requires discussion between the investigator and the medical monitor. Supportive measures consistent with optimal patient care may be given throughout the study.

8.5 Precautions and Restrictions

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

It is unknown what effects TAK-981 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. If a female patient becomes pregnant during TAK-981 treatment, TAK-981 should be stopped, and the patient should be informed about

the potential hazards to the fetus. If a male patient's partner becomes pregnant during TAK-981 treatment, she should be informed of the potential hazards to the fetus. In either case, the pregnancy should be followed until the final pregnancy outcome is known.

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 6 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.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 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.)

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.

8.6 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, G-CSF, 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. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.2.4.

In the sections below is 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. This guidance is not expected to replace investigator judgment in the management of AEs.

8.6.1 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.

8.6.2 Diarrhea

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

8.6.3 Anemia, Thrombocytopenia, or Neutropenia

Please refer to Table 8.c 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. It should be noted that initiation of myeloid growth factors (eg, G-CSF) for patient enrolled in dose escalation are not allowed in Cycle 1 before confirmation of DLT. In case of a first event, a dose reduction is preferred over the usage of myeloid growth factors.

8.6.4 Infusion Site Care

Skin lesions, which may include inflammation or necrosis, represent a potential risk 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 ports is highly recommended. The 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.

8.6.5 Lymphopenia and Opportunistic Infection Prophylaxis

Because lymphopenia is an expected AE, patients may be at an increased risk of opportunistic pathogens. TAK-981 lymphopenia is expected to be fully reversible and limited in time, therefore

no antibiotic or antiviral primary prophylaxis is indicated. It is also not known if all lymphocyte populations or just a subset are affected. Follow up with standard hemograms and serial CD4/8 counts will help to make clinical decisions about the risk of immunosuppression. However, in the event of long lasting lymphopenia, pneumocystis, or herpes zoster infection, prophylaxis can be started at investigator's discretion.

8.6.6 IRRs

Although TAK-981 is not a biological, its immune activating properties may produce AEs in the category of IRRs. If they 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. The patient should be closely monitored until recovery of symptoms. The patient will be permanently discontinued from the trial 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. If a patient presents signs and symptoms compatible with infusion reaction, and at investigator discretion, premedication can be instituted for the rest of the treatment.

8.6.7 CRS

CRS is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. CRS should be diagnosed and managed following institutional guidelines. CRS should be graded following the ASTCT Consensus Grading for CRS [1]. Investigators should try to differentiate CRS syndrome from other IRRs. Recommendations for management of CRS are shown in Table 8.d and can be implemented at the investigator's discretion.

Table 8.d CRS Management Recommendations and TAK-981 Dose Modification

ASTCT Consensus Grade	CRS Management Recommendations and TAK-981 Dose Modification
Grade 1: Fever [a] (≥38°C)	• Monitor fluid status. • Supportive care: antipyretics, analgesics. *TAK-981 dosing* • Continue TAK-981 at the same dose level.
Grade 2: Fever [a] (≥38°C) with hypotension not requiring vasopressors; and/or [b] requiring low-flow [c] nasal cannula	As per Grade 1 and: • Closely monitor all organ functions, including cardiac function. • IV fluid bolus. • Supportive care. *TAK-981 dosing* • Withhold TAK-981 until recovers to ≤Grade 1. • Once recovered, restart TAK-981 at the same dose level. A maximum of 2 consecutive TAK-981 doses can be skipped; otherwise TAK-981 must be permanently discontinued.
Grade 3: Fever [a] (≥38°C) with hypotension requiring a vasopressor with or without vasopressin; and/or [b] 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. *TAK-981 dosing* • Withhold TAK-981 until recovers to ≤Grade 1. • If recovered within 2 weeks, reduce TAK-981 by 1 dose level. A maximum of 2 consecutive TAK-981 doses can be skipped; otherwise TAK-981 must be permanently discontinued.
Grade 4: Fever [a] (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin); and/or [b] 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. *TAK-981 dosing* • 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; ICU: intensive care unit; O_2: supplemental oxygen.
ASTCT consensus grade adapted from Lee et. al. 2019[1]; CRS management recommendations are adapted from Neelapu et al, 2018 [59] 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.

8.7 Blinding and Unblinding

This is an open-label study.

8.8 Description of Investigational Agents

TAK-981 drug product has been developed as an injection, for IV use (solution for infusion). [redacted] It is packaged in a glass vial nominally containing 10.5 mL of TAK-981 sterile solution, which includes 0.5 mL overfill.

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.

8.9 Preparation, Reconstitution, and Dispensation

The reconstituted product will be administered by IV infusion over 1 hour. 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.

8.10 Packaging and Labeling

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

8.11 Storage, Handling, and Accountability

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.

8.12 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, the advertisements 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 an open-label study. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the sponsor and obtain the sponsor's approval to enroll the patient. Once the sponsor reviews and approves the patient for enrollment, the patient cohort and treatment group will be assigned via interactive response technology.

9.4 Study Procedures

9.4.1 Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, EOT visit, and follow-up visit, 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 and procedures may occur up to 3 days before the scheduled day due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).

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

9.4.1.1 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.

9.4.1.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.4.1.3 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 9.4.1.9.

Any available pathology/cytogenetic/mutational and tumor genomic information for all patients should be reported in the eCRF.

9.4.1.4 Physical Examination

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

9.4.1.5 Patient Height and Weight

Height and body weight will be measured at the times specified in the SOE (Appendix A).

9.4.1.6 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).

9.4.1.7 Vital Signs

Vital sign measurements, including systolic and diastolic blood pressure, heart rate, and temperature, will be assessed as specified in the SOE (Appendix A).

9.4.1.8 Pregnancy Test

A serum or urine pregnancy test will be obtained for women of childbearing potential at screening, Day 1 of each cycle, and at the EOT visit. 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.

9.4.1.9 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 8.3 for a list of medications and therapies that are prohibited during the study.

9.4.1.10 AEs

Monitoring of AEs, serious and nonserious, will be conducted 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.

9.4.1.11 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.

9.4.1.12 Posttreatment Follow-up

Patients in Phase 1 who discontinue study treatment for reasons other than disease progression will continue PFS follow-up every 12 (±1) weeks from the EOT visit for up to 12 months or until a discontinuation criterion is met (Section 9.7). Patients in follow-up will continue with disease assessment as described in Section 9.4.1.15. Follow-up visits for patients who discontinue study treatment for reasons other than disease progression (PFS follow-up) should be conducted at the site when possible.

Patients in Phase 2 who discontinue or complete treatment will be followed for survival every 12 (±1) weeks from the EOT visit for up to 12 months after the last patient in the cohort discontinues or completes treatment, or until loss of follow-up, consent withdrawal, death, study termination, or until >70% of patients in the cohort have progressed, whichever occurs first. Patients who discontinue study treatment for reasons other than disease progression or initiation of new anticancer treatment will be followed for PFS and will continue with disease assessment as described in Section 9.4.1.15. Visits for patients in follow-up who have not progressed or initiated new anticancer treatment should be conducted at the site when possible. For patients who have who have progressed or initiated new anticancer treatment, survival status and collection of new anticancer therapy will be obtained remotely. For all patients, information on new anticancer therapy will be collected.

9.4.1.13 Cardiac Monitoring

9.4.1.13.1 12-Lead ECGs and Left Ventricular Ejection Fraction

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 5 minutes. [redacted] 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 left ventricular ejection fraction (LVEF) measured by echocardiography or multiple-gated acquisition (MUGA) scan will be performed at times specified in the SOE (Appendix A). The MUGA scan or the echocardiographic estimate of the LVEF as an alternative to MUGA scan, should be performed at screening to ensure patient eligibility. From Cycle 1 onwards, a ±7-day window is allowed for this test. Any findings from echocardiography/MUGA LVEF determinations will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline. 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.

9.4.1.13.2 [redacted]

9.4.1.14 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.

9.4.1.14.1 Chemistry, Hematology, Coagulation, Urinalysis, and Tumor Markers

Blood samples for analysis of the chemistry and hematology parameters (Table 9.a), urine samples for analysis of the parameters (Table 9.b), and tumor markers (Table 9.c) will be obtained as specified in the SOE (Appendix A). They will be performed locally only.

Table 9.a Chemistry, Hematology, and Coagulation Tests

Hematology	Serum Chemistry	Coagulation
Hematocrit	Albumin	Activated partial thromboplastin time (aPTT)
Hemoglobin	Alkaline phosphatase	Prothrombin time (PT)
Leukocytes with differential	Alanine aminotransferase	Fibrinogen
Neutrophils	Aspartate aminotransferase	
CD4/CD8 count and ratio	Bilirubin (total)	
Platelet count	Blood urea nitrogen (BUN)	
	Calcium	
	Bicarbonate ($HCO3^-$) or carbon dioxide (CO_2)	
	Creatinine	
	Standard C-reactive protein	
	Chloride	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	Urate	

Table 9.b Urinalysis Tests

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

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 [60] 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.

Table 9.c Serum Tumor Markers

Colon Cancer	Cervical Cancer
Carcinoembryonic antigen (CEA)	Cancer antigen 15-3 (CA 15-3)
Cancer antigen 19-9 (CA 19-9)	Cancer antigen 125 (CA 125)

Blood sample collection for tumor markers during Phase 2 only.

9.4.1.14.2 Immunosafety Markers

Blood samples for the analysis of autoimmune endocrinopathies as shown in Table 9.d will be obtained as specified in the SOE (Appendix A). They will be performed locally only.

Table 9.d Immunosafety Determinations in Serum

Serum Chemistry	
Thyroid-stimulating hormone (TSH)	Free thyroxine (FT4)
	Adrenocorticotropic hormone (ACTH)

9.4.1.15 Disease Assessment

Patients will undergo computed tomography (CT) and/or MRI scans, and ^{18}fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging to assess disease response and progression, using RECIST v1.1 criteria for solid tumors [61] or the Lugano criteria for lymphoma response from the Cheson 2014 [62]. For this study CT and/or MRI scans should be acquired with at least IV contrast. CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. The

imaging modalities used for a patient should remain consistent throughout the study. If contrast-enhanced CT scans are contraindicated for a particular patient, a noncontrast CT of the chest, in addition to contrast-enhanced abdomen and pelvis MRIs should be acquired, if possible. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation. In addition, nonmeasurable disease and new lesions will be documented and their status evaluated. For lymphoma patients FDG-PET imaging is required so that the avidity of the disease burden can also be scored according to the Lugano classification. Objective assessments of the disease burden (target, nontarget, and potential new lesions) will be performed at each time point as described in the SOE (Appendix A). Radiographic images will be maintained at the site and can be requested by the sponsor at a later date for centralized review of the images.

Bone scans should be collected as clinically indicated.

Imaging tests performed before the screening consent date, if of diagnostic quality, may be used as screening tests if the C1D1 is planned within the 28 days after the date of the test.

9.4.1.16 Biomarker, Pharmacodynamic, and PK Samples

9.4.1.16.1 Primary Specimen Collection

The primary specimen to be collected are shown in Table 9.e. Collection of samples [redacted] are dependent on local guidelines and regulations (including feasibility of sample export), as well as IRB/independent ethics committee (IEC) approval.

Table 9.e Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
Archival (Banked) Tumor Tissue Sample	FFPE block FFPE slides	DNA RNA		Biomarker measurements	Required if sample is available
Fresh Tumor Tissue Biopsy Sample	Fresh tumor tissue	FFPE block/slides	DNA RNA	Biomarker measurements	Mandatory during Phase 2 stage 1 [a]
Fresh Skin Tissue Biopsy Sample	Fresh Skin Tissue	FFPE block FFPE slides		Biomarker measurements	Mandatory Phase 1 only
[redacted]					
Blood Sample for Flow Cytometry	Blood	Cells		Biomarker measurements	Mandatory Phase 1 only
[redacted]					
Blood Sample for TAK-981 PK	Blood			PK Measurements	Mandatory
Plasma Sample for TAK-981 PK	Plasma			PK Measurements	Mandatory
Urine Sample for TAK-981 PK	Urine			PK Measurements	Mandatory [b]

[redacted]; FFPE: formalin-fixed, paraffin-embedded; [redacted]; PK: pharmacokinetic.

[a] Except for Phase 2 stage 1, paired tumor biopsies are optional.

[b] Whole blood and urine collection will only be collected in dose levels 60 mg and 120 mg.

9.4.1.16.2 Skin Biopsy Measurements

All skin punch biopsies should be obtained from the upper back following institutional guidelines from all patients in Phase 1 at prespecified time points, as outlined in the SOE (Appendix A), to detect the formation of SUMO-TAK-981 adducts and inhibition of SUMO2/3. A decision to stop skin punch biopsies collection may take place should sufficient data related to target engagement and SUMO2/3 inhibition be generated.

9.4.1.16.3 Tumor Tissue

9.4.1.16.3.1 Banked Tumor

Banked formalin fixed paraffin-embedded tumor tissue or ideally 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected, if available, from all enrolled patients in both the dose escalation and Phase 2 part [redacted] See the laboratory manual for details.

9.4.1.16.3.2 Fresh Paired Tumor Biopsy

[redacted] To inform the translational endpoints and decision making, pretreatment and on treatment biopsies are compulsory for patients enrolled during Phase 2 stage 1 of the study and are optional for but encouraged from patients enrolled during Phase 1 or Phase 2 stage 2 of the study.

- The pretreatment (screening) tumor biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of TAK-981.
- The on-treatment biopsy will be obtained during Phase 2 stage 1 and collected at Cycle 2, Day 8 (C2D8) (+7 days). On-treatment tumor biopsies taken outside Phase 2 stage 1 should be collected on C2D8 (+7 days) whenever possible.

The accessible lesion biopsy should not have been previously designated as the only target lesion for measurable disease or located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and on treatment whenever possible. On treatment biopsy collection visits may be changed should emerging data be supportive for that change.

Note: The lesion must be accessible for a biopsy procedure as assessed by the investigator.

9.4.1.16.4 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual. Plasma, blood, and urine samples for PK will be collected at the time points specified in Appendix A. Blood/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, blood, urine, and/or ECG samples may be modified during the study based on emerging PK data [redacted] A protocol amendment is not necessary for such modifications.

Plasma, blood, and urine collected in this study will be used to measure the level of TAK-981 [redacted]

9.4.1.16.5 Pharmacodynamic Measurements

The pharmacodynamics specimen collection time points are displayed in Appendix A. Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

9.4.1.16.5.1 Blood Samples for Adduct Formation and SUMO2/3 Inhibition

Blood samples will be collected to detect the formation of SUMO-TAK-981 adducts and inhibition of the SUMOylation pathway in distinct subpopulations of the immune system including: B and T lymphocytes, NK cells, monocytes, and granulocytes.

9.4.1.16.5.2 [redacted]

9.4.1.16.5.3 [redacted]

9.4.1.16.5.4 [redacted]

9.4.1.16.5.5 [redacted]

[redacted]

9.4.1.16.5.6 [redacted]

[redacted]

9.4.1.16.6 [redacted]

[redacted]

9.5 Completion of Study Treatment (for Individual Patients)

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

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.
- Withdrawal by patient.
- Study terminated by the sponsor.
- Lost to follow-up.
- Completion of follow-up.
- Progressive disease (only in dose escalation).
- Start of new systemic treatment (only in dose escalation).
- Transfer of patient to a TAK-981 long-term safety study, single-patient investigational new drug application, or similar program.

Once study has been completed, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A).

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database after the EOT visit 30 days after last dose is completed.

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 may be discontinued for any of the following reasons:

- AE that leads to TAK-981 discontinuation.
- Major protocol deviation.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Death.
- Progressive disease.
- Occurrence of a DLT for patients in dose escalation (exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit and risk assessment).
- Symptomatic deterioration.
- Initiation of another systemic anticancer treatment.
- Treatment completion: the patient completes 1 year of treatment and continuation is not approved.
- CR (after discussion with sponsor).
- Lack of benefit.
- Clinical progression.

The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients enrolled in Phase 1 dose escalation may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) until progressive disease occurs. All patients in Phase 2 will be followed for OS as outlined in the SOE (Appendix A).

During Phase 1 dose escalation, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced. Patients will not be replaced during the Phase 2 part of the study.

In the case of study termination by the sponsor, eligible patients in dose escalation or cancer treatment expansion may have continued access to TAK-981 as described in Section 6.4.5.

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.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment 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 addition to the above examples, any event that the investigator considers to be medically important will be considered an SAE.

Note that any death, whether due to side effects of the treatment, progressive disease, or other causes, is considered an SAE.

Hospitalization for previously planned procedure or convenience will not be considered a reportable SAE.

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 [1]. 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.

10.1.4 Adverse Events of Special Interest Definition

An adverse event of special interest (AESI) is an AE of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the

investigator to Takeda may be appropriate. Such events may require further investigation to characterize and understand them, and instructions regarding how and when AESIs should be reported to Takeda are provided in Section 10.2. CRS will be treated as an AESI.

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 [1]. 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?

AESI Reporting:

All AESIs regardless of seriousness or causality must be reported by the investigator to the sponsor within 72 hours of the investigator's becoming aware of the event. This will be done by transmitting an EDC form. If the AESI meets any of the seriousness criteria mentioned in Section 10.1.3, the event will be reported to the sponsor within 24 hours of the investigator's becoming aware of the event. All nonserious AESIs are captured in only the clinical database.

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.
- 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).
- AESIs will be reported and monitored as stated in the SAE section.

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 6 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	Contact	Email
TAK-981	Takeda	ctmcompliance@takeda.com

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

10.6 Safety Reporting to Investigators, IRBs, 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, study medical monitor, and sponsor safety monitor will regularly review safety data to ensure patients' safety throughout the study and make decisions on dose escalation, safety lead-in, and continued enrollment.

11.2 IDMC

For Phase 2 cancer treatment expansion cohort, an IDMC will be established to monitor safety and assess benefit/risk throughout the conduct of these portions 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 physicians 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 Phase 2 cancer treatment expansion cohorts. IDMC meetings will be held on a periodic basis as defined in the IDMC charter, at the end of each stage of the Phase 2, and for the interim

analysis for safety. Ad hoc IDMC meetings will be held to evaluate safety 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 MedDRA. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

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

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, 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 its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The 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 its designee. 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 and analytical plan (SAP) for dose escalation and cancer treatment expansion will be prepared and finalized before database lock. This document will provide further details regarding the respective definition of analysis variables and analysis methodology to address all study objectives.

13.2 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

13.2.1 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 in dose escalation who receive all Cycle 1 doses of TAK-981 without experiencing a DLT or who have a DLT during Cycle 1 of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Tumor 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 was discontinued due to symptomatic deterioration or death before a postbaseline evaluation happens, 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 at least 1 on-treatment 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]

13.2.2 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.

13.2.3 Efficacy Analysis

13.2.3.1 Primary Efficacy Analysis

Phase 1:

Efficacy is not the primary objective for this study in the Phase 1 portion.

In the Phase 1 portion of this study, efficacy parameters such as ORR, DCR, DOR, TTR, TTP, and PFS will 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 response assessments based on RECIST v1.1 for solid tumors or Lugano classification for lymphomas [62]. The formal hypotheses (see Section 13.4.1) of ORR will be tested for each cancer type.

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 analysis set.

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

13.2.3.2 Secondary Efficacy Analysis

ORR is a secondary efficacy endpoint for the Phase 1 portion only. Similarly, with the primary analysis for the Phase 2 portion, estimates of the ORR (CR + PR) will be presented with 2-sided 95% exact binomial CIs.

Other secondary efficacy endpoints for both Phase 1 and Phase 2 portions include DCR, DOR, TTR, TTP, PFS, and OS.

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

DCR is defined as the proportion of patients who achieve SD or better (determined by the investigator) >6 weeks during the study in the response-evaluable population.

TTR is defined as the time from the date of first study drug administration to the date of first documented PR or better by the investigator for responders. Patients without documentation of progressive disease will be censored at the date of the last response assessment that is PR or better.

TTP is defined as the time from the date of the first dose administration to the date of first documented progressive disease. Patients without documentation of progressive disease at the time of analysis will be censored at the date of last response assessment. Patients who take

alternative antineoplastic therapy before progression or who die during treatment will also be censored at the date of last response assessment.

PFS is defined as the time from the date of the first dose administration to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. Patients without documentation of progressive disease will be censored at the date of the last response assessment that is SD or better.

OS is defined as the time from the date of the first dose administration to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

DOR, TTP, TTR, PFS and OS will be summarized descriptively using Kaplan-Meier method. TTP, PFS, and OS will be analyzed for the safety analysis set. DCR will be analyzed using a method similar to that used for ORR.

13.2.4 PK Analysis

In Phase 1, PK parameters will be estimated using noncompartmental methods with Phoenix WinNonlin. The PK parameters will be estimated from the concentration-time profiles for the PK population. The following PK parameters will be determined, as permitted by data:

- C_{max}.
- t_{max}.
- AUC_{last}.
- AUC_{∞}.
- $t_{1/2z}$.
- 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 sparse PK data collected after Cycle 1 will be presented in listings and tabulated using summary statistics.

The 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.

13.2.5 Pharmacodynamic Analysis

The analysis of [redacted] 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 help to determine the single agent RP2D. In addition, candidate response biomarkers will be evaluated.

13.2.6 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. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 and for determination of BED.

To determine the appropriateness of the BED/schedule as an RP2D/schedule, a totality of evidence approach will be used that will integrate all available data from the dose escalation and expansion phases of the study including:

1. Multicycle safety/tolerability of TAK-981.
2. Single and multiple dose PK of TAK-981.
3. Single and multiple dose pharmacodynamic biomarkers of TAK-981 (in circulation, skin, [redacted]
4. Antitumor response with TAK-981 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 addition, the PK-pharmacodynamic data collected in the study may be used to inform a quantitative systems pharmacology (QSP) 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 TAK-981 clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and QSP modeling may not be presented in the clinical study report for this study but will be presented in a separate report.

13.2.7 [redacted]

[redacted]

13.2.8 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 MedDRA 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 statuses 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. The number and percentage of patients with clinically significant laboratory values will also be tabulated as appropriate.

All concomitant medications collected from the first dose of study drug throughout the study period will be classified to preferred terms according to the WHO Drug Dictionary.

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

13.3 Interim Analysis

The SMC will review accruing data to determine dose escalation and number of patients per cohort in the dose escalation phase (see Section 8.2.2).

13.4 Determination of Sample Size

13.4.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts

It is anticipated that up to approximately 70 patients will be enrolled in Phase 1 (dose escalation) and up to approximately 132 patients will be enrolled in Phase 2 cancer treatment expansion cohorts.

Dose Escalation Phase (Phase 1)

It is estimated that up to approximately 70 DLT-evaluable patients will be enrolled in this study for the dosing escalation of TAK-981 in Phase 1. A minimum of 3 patients per cohort will be enrolled in the starting dose cohort. In case of no DLT, an adaptive BLRM guided by the Escalation With Overdose Control principle will be used in successive escalation cohorts for purposes of dose escalation recommendations and estimation of the MTD. The logistic regression model will be adapted and updated after each group of patients enrolled in the current dose level cohort. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.16): under-dosing.
- [0.16, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The selection of the next recommended dose will be determined from BLRM along consideration of other safety, clinical, PK, and pharmacodynamic data.

The details of the BLRM are included in Appendix G. The details of dose-escalation are specified in Section 8.2.2.

Efficacy Evaluation Phase (Phase 2)

Once the MTD/BED is defined, up to approximately 132 response-evaluable patients with 6 specified types of solid tumors and 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 RECIST v1.1 [61] for patients with solid tumors and Lugano criteria [62] 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 [63] with the following hypotheses of ORR.

For solid tumor cohorts A, B, and C and lymphoma cohort D (Figure 6.a):

The hypotheses for stage 1 are the following:

H_0: ORR $< p_0$ where $p_0 = 15\%$

H_1: ORR $\geq p_0$ where $p_0 = 15\%$

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted) at stage 1, additional patients will be enrolled based on the number of responders in stage 1 and their data will be collected in the second stage.

The hypotheses at the end of stage 2 for a low desirable ORR, p1, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_1$ where $p_1 = 35\%$

H_1: ORR $> p_1$ where $p_1 = 35\%$

The hypotheses at the end of stage 2 for a high desirable response, p2, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_2$ where $p_2 = 45\%$

H_1: ORR $> p_2$ where $p_2 = 45\%$

Because it is desirable to have higher power for detecting more improvement of the new therapy (p_2 versus p_0), for solid tumor cohorts A, B, and C and lymphoma cohort D (Figure 6.a), assuming a power of 80% for high desirable response and 70% for low desirable response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 13.a).

Table 13.a Sample Size for Each Cohort and Each Stage (Solid Tumor Cohorts A, B, and C and Lymphoma Cohort D)

	Stage		Total Number of Patients in Each Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of stage 1				
Number of patients	7	19	19	0.1/70%
Number of responses [a]	≥2 and ≤4	≥5		
High response at the end of stage 1				
Number of patients	7	13	13	0.1/80%
Number of responses	≥5	≥6		

[a] Number of patients needed to respond to continue into stage 2 or have a positive result at the end of stage 2.
[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of stage 2 in order to claim treatment effect.

For lymphoma cohorts E and F (Figure 6.a):

The hypotheses for stage 1 are the following:

H_0: ORR $< p_0$ where $p_0 = 45\%$

H_1: ORR $\geq p_0$ where $p_0 = 45\%$

where p_0 is a very low, undesirable ORR.

If H_0 is rejected (and H_1 is accepted) at stage 1, additional patients will be enrolled based on the number of responders in stage 1 and their data will be collected in the second stage.

The hypotheses at the end of stage 2 for a low desirable ORR, p1, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_1$ where $p_1 = 65\%$

H_1: ORR $> p_1$ where $p_1 = 65\%$

The hypotheses at the end of stage 2 for a high desirable response, p2, are the following:

a) H_1 is accepted at stage 1, and

b) H_0: ORR $\leq p_2$ where $p_2 = 75\%$

H_1: ORR $> p_2$ where $p_2 = 75\%$

Similarly, for lymphoma cohorts E and F, assuming a power of 80% for high desirable response and 70% for low desirable response and 1-sided alpha of 0.1, the following number of patients is required for each cohort at each stage (Table 13.b).

Table 13.b Sample Size for Each Cohort and Each Stage (Lymphoma Cohorts E and F)

	Stage		Total Number of Patients in Each Cohort	1-Sided Alpha Level/Power
	Stage 1	Stage 2 [b]		
All cohorts				
Low response at the end of stage 1				
Number of patients	10	28	28	0.1/70%
Number of responses [a]	≥6 & ≤7	≥16		
High response at the end of stage 2				
Number of patients	10	16	16	0.1/80%
Number of responses	≥8	≥9		

[a] Number of patients needed to respond to continue into stage 2 or have a positive result at the end of stage 2.

[b] Maximum number of patients required for each cohort and number of responders that should be presented at end of stage 2 in order to claim treatment effect.

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, coronavirus disease 2019 [COVID-19]), remote electronic medical records access visits may be made (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, 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 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 ethics committee, 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 US Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct

the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator 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 must be constituted according to the applicable state and federal requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal wide Assurance number or comparable number assigned by the US 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 for approval. The IRB'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 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 ship drug 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. This may include notification to the IRB 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. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject

information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, 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 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible

websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants 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 or 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 SOE

Table A-1 SOE for Phase 1 Dose Escalation Treatment Cycles (21-Day Cycle)

Cycle		Cycle 1								Cycle 2					Cycle 3 and Subsequent Cycles					EOT [b]	PFS Follow-up [c]
Day	**Screening [a]**	**1**	**2**	**3**	**4**	**8**	**9**	**11**	**15**	**1**	**4**	**8**	**11**	**15**	**1**	**4**	**8**	**11**	**15**		
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics	X																				
Medical history	X																				
Physical examination [d]	X																				
Symptom-directed physical examination [e]										X					X					X	
Height	X																				
Weight	X									X					X					X	
ECOG performance status	X	X								X					X					X	
Vital signs [f]	X	X	X		X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	
12-Lead safety ECG [i]	X					X2														X	
[redacted]																					
Echocardiography/MUGA (LVEF) scan [k]	X									X					X					X	
Concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.																			X	
AE reporting	AEs will be recorded from the signing of ICF through 30 days after the last dose of study drug or start of subsequent anticancer therapy.																			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	X
Samples/Laboratory Assessments																					
Pregnancy test [l]	X	X								X					X					X	
Hematology/chemistry [m]	X	X			X [g]	X		X [g]		X	X [g]	X	X [g]		X	X [g]	X	X [g]		X	
Coagulation [m]	X	X								X					X						

Cycle		Cycle 1								Cycle 2					Cycle 3 and Subsequent Cycles					EOT [b]	PFS Follow-up [c]
Day	**Screening [a]**	**1**	**2**	**3**	**4**	**8**	**9**	**11**	**15**	**1**	**4**	**8**	**11**	**15**	**1**	**4**	**8**	**11**	**15**		
Urinalysis [m]	X	X			X [g]	X		X [g]		X	X [g]	X	X [g]		X					X	
Immunosafety markers (hormones) [n]		X													X					X	
Whole blood sample for adducts/conjugates (flow cytometry) [o]		X				X				X					X [p]		X [p]				
[redacted]																					
Urine collection for PK assessment [q]		X	X																		
Disease Assessment and Procedures																					
Disease assessment [r]	X	Every 8 weeks ±7 days (from C1D1 for the first 6 months and every 12 weeks ±7 days thereafter																		X [s]	X [t]
Tissue Samples																					
Fresh skin punch biopsy [u]	X					X															
Fresh tumor tissue biopsy [v]	X											X									
Banked tumor tissue [w]	X																				
Study Drug Administration																					
TAK-981 administration [x]		X			X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]		

AE: adverse event; COVID-19: coronavirus disease 2019; CT: computed tomography; CxDx: Cycle x, Day x; DLT: dose-limiting toxicity; ECG: electrocardiography; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: end-of-treatment; FDG-PET: ^{18}fluorodeoxyglucose–positron emission tomography; ICF: informed consent form; MRI: magnetic resonance imaging; MUGA: multiple-gated acquisition; PFS: progression-free survival; PK: pharmacokinetics; LVEF: left ventricular ejection fraction; MUGA: multiple-gated acquisition; RECIST v1.1: Response Evaluation Criteria in Solid Tumors Version 1.1; SAE: serious adverse event; SOE: schedule of events; X2: assessment performed twice.

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. **Laboratory assessments and procedures may occur up to 3 days before the scheduled day due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons). 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.**

[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 discontinue TAK-981 treatment early should complete the EOT visit 30 (+10) days after the last dose of TAK-981 or before starting a new systemic treatment. See Section 9.6.

[c] Patients who discontinue study treatment for reasons other than disease progression will continue PFS follow-up every 12 (±1) weeks from the EOT visit for up to 12 months or until a discontinuation criterion is met (Section 9.7). Follow-up visits should be conducted at the site when possible.

[d] Complete physical exam at screening. If a complete physical exam was performed more than 3 days before C1D1, the exam should be performed again.

[e] The symptom-directed physical examination will be conducted within 3 days before dosing on Day 1 of each treatment cycle and at the EOT/early termination visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[f] From C1D1 onwards, perform and document vital signs measurement (blood pressure, heart rate, and temperature) immediately before the start of the infusion, and immediately after the end of infusion. Vitals will be monitored during the following 6 hours after the end of the infusion and before the patient is discharged, and at any time if the patient presents symptoms during the 18-hour hospitalization. If an AE is observed, extended monitoring of vital signs can be conducted as medically indicated. Outside C1D1, vital signs need to be documented as stated above, and patients monitored up to 4 hours after the end of the infusion. From C2 onwards, if no infusion reaction is observed in the first cycle, the patient can be discharged from the site per investigator discretion. Blood pressure should be determined with the patient in a supine position after the patient has been at rest for 5 minutes.

[g] For patients enrolled on a less dense schedule (eg, TAK-981 on Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 every 21 days), this test, procedure, or dosing may not be performed.

[h] For patients enrolled in the dosing schedule of Day 1, Day 8, and Day 15 every 21 days only, this test or procedure must be performed.

[i] Single safety ECGs will be collected predose at screening and C1D8 post–end-of-infusion (+1-hour window) on C1D8 and at EOT. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[redacted]

[k] The MUGA (LVEF) scan should be performed at screening to ensure patient eligibility. Echocardiographic estimate of the LVEF can be measured as an alternative to MUGA scans. From C3 onwards, the assessment of LVEF will be repeated every 3 cycles and at EOT. From C2 onwards, a ±7-day window is allowed for this test.

[l] A serum or 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 is administered (ie, within the 3 days before C1D1), or as otherwise required by local regulations. From C2 onwards, serum or urine pregnancy test will be performed on Day 1 of each cycle and at the EOT visit.

[m] Hematology, chemistry, coagulation tests, and urinalysis may be performed up to 3 days prior to C1D1 during the screening period unless otherwise notified. From C1D4 onwards, hematology, chemistry, and coagulation tests and urinalysis may be performed 24 hours before the visit. From Cycle 3 onwards, urine tests will be taken only the first day of each cycle and at end-of-treatment. For specifics, see Section 9.4.1.14.1.

[n] Immunosafety determinations include thyroid-stimulating hormone, free thyroxine, and adrenocorticotropic hormone measured in blood on C1D1 and repeated at the beginning of each cycle from C3 until C6, every other cycle afterwards, and at the EOT.

[o] Time points for blood and plasma samples for candidate biomarkers will be collected as specified in Table A-3.

[p] Samples will be collected on Cycles 3, 6, and 9 only.

[q] Time points for plasma, whole blood, and urine samples for PK analysis will be collected as specified in Table A-2. Whole blood and urine only to be collected from patients enrolled in dose levels 60 mg and 120 mg, in the Day 1, Day 4, Day 8 and Day 11 every 21 days, dosing schedule.

[r] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis in addition to an FDG-PET scan for lymphoma patients must be acquired at screening. 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. Contrast-enhanced CT or MRI and FDG-PET (for lymphoma patients) should be performed every 8 weeks (±7 days) from C1D1 for the first 6 months and every 12 weeks (±7 days) thereafter, or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (ie, administration of TAK-981) The same imaging modality (contrast-enhanced CT or MRI and FDG-PET scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients as clinically indicated. See Section 9.4.1.15. Response will be determined according to RECIST v1.1 for patients with solid tumors or Lugano criteria for patients with lymphoma.

[s] At EOT, tumor assessments will be performed only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

[t] During PFS follow-up, disease assessment will be performed every 12 weeks (±7 days), or more frequently if clinically indicated. See Section 9.4.1.15.

[u] The skin punch at screening should be performed within 14 days before the first dose of study drug on C1D1 for all patients in the Phase 1 cancer dose-escalation portion of the study. The C1D8 skin punch biopsy should be done 2 (±1) hour after the end of TAK-981 infusion. A decision to stop skin punch biopsies collection may take place should sufficient data related to target engagement and SUMO2/3 inhibition be generated.

[v] Screening and on-treatment paired tumor biopsies are encouraged but optional for patients enrolled during Phase 1. The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of drug. On-treatment tumor biopsies should be collected on C2D8 (+7 days). Refer to Section 9.4.1.16.3 for details.

[w] Banked formalin-fixed paraffin-embedded tumor tissue or unstained slides of the tumor tissue. Please refer to Section 9.4.1.16.3 for details.

[x] Initially, TAK-981 will be administered intravenously on Days 1, 4, 8, and 11 of a 21-day cycle. Less intensive schedules of TAK-981 (eg, on Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 every 21 days). For the first infusion (C1D1) of TAK-981 during dose escalation, every patient needs to be hospitalized for drug administration and overnight observation. The patient can be discharged from overnight observation (a minimum of 18 hours after the end of infusion) only if there are no signs and symptoms of acute toxicity, such as fever or significant changes in blood pressure and/or heart rate. Hospitalization is not required if the patient is part of an expanded dose cohort after the first 3 patients in a dose level or expansion of a previously cleared dose level and if the infusion reaction risk is considered low based on previous experience. 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. For patients in the DLT-evaluation period (Cycle 1) a maximum of 1 dose reschedule is allowed. At least 72 hours should elapse between consecutive doses of TAK-981. For further details on TAK-981 administration, refer to Section 8.1.

Table A-2 Phase 1 Dose Escalation: Serial Whole Blood, Plasma, and Urine PK [redacted]

	Cycle 1					Cycle 2	
	Day 1			Day 4	Day 8	Day 1	Day 8
[redacted]	PK (Whole Blood and Plasma) [b]	Urine [b]		PK (Plasma only)	PK (Plasma only)	PK (Plasma only)	PK (Plasma only)
Predose (within 1 h before the start of infusion)	X1	X1 [c]		X1	X1	X1	X1
End of infusion (±10 min)	X1	0-24 h pooled urine [d]		X1	X1	X1	X1
0.5 h after end of infusion (±10 min)	X1				X1		
1 h after end of infusion (±20 min)	X1				X1		
2 h after end of infusion (±30 min)	X1				X1		
4 h after end of infusion (±30 min)	X1				X1		
8 h after end of infusion (±30 min)	X1				X1		
24 h after end of infusion (±1 h)	X1				X1		
48 h after end of infusion (±1 h)	X1						

[redacted]; PK: pharmacokinetic.

[redacted]

[b] Whole blood and urine collection will only be collected in DLs 60 mg and 120 mg.

[c] Patients will void their bladders before dosing. This pre-dose urine will not be collected for bioanalysis.

[d] Urine will be pooled from start of infusion up to 24 hours after end of infusion. Urine will be collected in refrigerated containers during the collection period from Cycle 1 Day 1 into Cycle 1 Day 2. Cumulative urine volume collected over the 0-24 hour collection period will need to be recorded. An aliquot of the urine sample will be frozen and shipped to the bioanalytical laboratory for bioanalysis.

Table A-3 Phase 1 Dose Escalation: Biomarker Sample Collection

	Screening	C1D1					C1D8						C2D1	C2D8	C3+D1	C3+D8
		Predose	1 h post-EOI (±20 min)	4 h post-EOI (±30 min)	8 h post-EOI (±30 min)	24 h post-EOI (±60 min)	Predose	1 h post-EOI (±20 min)	2 h post-EOI (±60 min)	4 h post-EOI (±30 min)	8 h post-EOI (±30 min)	24 h post-EOI (±60 min)	Predose	+7 days	Predose	Predose
Archival (Banked) Tumor Tissue Sample	X															
Fresh Tumor Tissue Biopsy Sample [a]	X													X		
Fresh Skin Punch Tissue Biopsy Sample	X								X							
[redacted]																
Whole Blood Sample Adducts/Conjugates (flow cytometry) [c]		X	X	X	X		X	X		X	X		X		X	X
[redacted]																

C3+: Cycle 3, Cycle 6, and Cycle 9; EOI: end of infusion. "Post-EOI" refers to end of TAK-981 infusion.

[a] The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of the drug. Screening and on-treatment biopsies are compulsory for patients enrolled during Phase 2 stage 1 portion of the study. For all other patients, paired fresh tumor biopsies are encouraged but optional. On-treatment tumor biopsies taken outside Phase 2 stage 1 should be collected on C2D8 (+7 days) whenever possible or at another timepoint per investigator discretion. The accessible lesion biopsy should not have been previously designated as the only target lesion for measurable disease or being located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and during treatment whenever possible. Collection timing of the on-treatment biopsy may be changed should data collected during the study would be supportive of such a change. A decision to stop tumor biopsies collection may take place should sufficient tumor-related data be generated.

[redacted]

[c] Whole blood sample for adduct/conjugates will be collected during Phase 1 only.

Table A-4 SOE for Phase 2 Cancer Treatment Expansion Cohorts Treatment Cycles (21-Day Cycle)

Cycle		Cycle 1								Cycle 2					Cycle 3 and Subsequent Cycles					EOT [b]	Survival Follow-up [c]
Day	**Screening [a]**	**1**	**2**	**3**	**4**	**8**	**9**	**11**	**15**	**1**	**4**	**8**	**11**	**15**	**1**	**4**	**8**	**11**	**15**		
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics	X																				
Medical history	X	X																			
Survival Status																					X
Next anticancer treatment																					X
Physical examination [d]	X																				
Symptom-directed physical examination [e]										X					X					X	
Height	X																				
Weight	X									X					X					X	
ECOG performance status	X	X								X					X					X	
Vital signs [f]	X	X			X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	
12-Lead safety ECG [i]	X	X2				X2				X2		X2			X2					X	
Echocardiography/MUGA (LVEF) scan [j]	X									X					X					X	
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first																			X	
AE reporting	AEs will be recorded from the signing of ICF through 30 days after the last dose of study drug or start of subsequent anticancer therapy.																			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	X

Cycle		Cycle 1								Cycle 2					Cycle 3 and Subsequent Cycles					EOT [b]	Survival Follow-up [c]
Day	**Screening [a]**	**1**	**2**	**3**	**4**	**8**	**9**	**11**	**15**	**1**	**4**	**8**	**11**	**15**	**1**	**4**	**8**	**11**	**15**		
Samples/Laboratory Assessments																					
Pregnancy test [k]	X	X								X					X					X	
Hematology/chemistry [l]	X	X								X					X					X	
Coagulation [l]	X	X								X					X						
Urinalysis [l]	X	X								X					X					X	
Tumor markers [l]		X								X					X						
Immunosafety markers (hormones) [m]		X													X					X	
[redacted]																					
Plasma samples for PK		X			X	X				X		X									
Disease Assessment and Procedures																					
Disease assessment [r]	X	Every 8 weeks ±7 days (from C1D1 for the first 6 months and every 12 weeks ±7 days thereafter																		X [s]	X [t]
Tissue Samples																					
Fresh tumor tissue biopsy [u]	X											X									
Banked tumor tissue [v]	X																				
Study Drug Administration																					
TAK-981 administration [w]		X			X [g]	X		X [g]	X [h]	X	X [g]	X	X [g]	X [h]	X	X [g]	X	X [g]	X [h]		

AE: adverse event; [redacted]; COVID-19: coronavirus disease 2019; CT: computed tomography; CxDx: Cycle x, Day x; ECG: electrocardiogram, electrocardiographic, electrocardiography; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOT: end-of-treatment; FDG-PET: ^{18}fluorodeoxyglucose–positron emission tomography; ICF: informed consent form; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multiple-gated acquisition; [redacted]; PK: pharmacokinetics; RECIST v1.1: Response Evaluation Criteria in Solid Tumors Version 1.1; SAE: serious adverse event; SOE: schedule of events; X2:, assessment performed twice.

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 **Laboratory assessments and procedures may occur up to 3 days before the scheduled day due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons). 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.**

[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 discontinue TAK-981 treatment early should complete the EOT visit 30 (+10) days after the last dose of TAK-981 or before starting a new systemic treatment. See Section 9.6.

[c] Patients who discontinue or complete treatment will be followed for survival every 12 (±1) weeks from the EOT visit for up to 12 months after the last patient in the cohort discontinues or completes treatment, or until loss of follow-up, consent withdrawal, death, study termination, or until > 70% of patients in the cohort have progressed, whichever occurs first. Patients who discontinue study treatment for reasons other than disease progression or initiation of new anticancer treatment will be followed for PFS and will continue with disease assessment as described in Section 9.4.1.15 and in the SOE; follow-up visits for patients these patients should be conducted at the site when possible. For patients who have who have progressed or initiated new anticancer treatment, survival status and collection of new anticancer therapy will be obtained remotely. See Section 9.7.

[d] Complete physical exam at screening. If a complete physical exam was performed more than 3 days before C1D1, the exam should be performed again.

[e] The symptom-directed physical examination will be conducted within 3 days before dosing on Day 1 of each treatment cycle and at the EOT/early termination visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[f] On C1D1,vital signs (blood pressure, heart rate, and temperature) will be measured and documented immediately before the start of the infusion and immediately after the end of infusion. Patients will be monitored for up to 4 hours after the end of infusion. Outside C1D1, vitals will be monitored immediately before the start of infusion and after the end of infusion, and if no infusion reaction is observed, patients will be discharged from the site per investigator discretion Blood pressure should be determined with the patient in a supine position after the patient has been quiet for 5 minutes.

[g] For patients enrolled on a less dense schedule (eg, TAK-981 on Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 every 21 days), this test, procedure, or dosing may not be performed.

[h] For patients enrolled in the Day 1, Day 8, and Day 15 every 21 days only, this test or procedure must be performed.

[i] Single safety ECGs will be collected at screening, pre-TAK-981 dose and post-TAK-981 EOI (+1-h window) on Days 1 and 8 of Cycle 1 and Cycle 2. From Cycle 3 onward, pre-TAK-981 dosing and post-TAK-981 EOI (+1-h window) ECGs will be collected on Day 1 of every other cycle. 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.

[j] The MUGA (LVEF) scan should be performed at screening to ensure patient eligibility. Echocardiographic estimate of the LVEF can be measured as an alternative to MUGA scans. From C3 onwards, the assessment of LVEF will be repeated every 3 cycles and at EOT. From C3 onwards, a ±7-day window is allowed for this test.

[k] A serum or 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 is administered (ie, within the 3 days before C1D1), or as otherwise required by local regulations. From C2 onwards, serum or urine pregnancy test will be performed on Day 1 of each cycle and at the EOT visit.

[l] Hematology, chemistry, coagulation, tumor markers (CEA and CA 19-9 in colon cancer patients, CA 15-3 and CA 125 in cervical cancer patients), and urinalysis may be performed up to 3 days prior to C1D1 during the screening period unless otherwise notified. From C2 onwards, hematology, chemistry, tumor markers, coagulation tests and urinalysis may be performed 24 hours before the visit. For specifics, see Section 9.4.1.14.1

[m] Immunosafety determinations include thyroid-stimulating hormone, free thyroxine, and adrenocorticotropic hormone measured in blood on C1D1 and repeated at the beginning of each cycle from C3 until C6, every other cycle afterwards, and at the EOT.

[redacted]

[o] Samples will be collected on Cycles 3, 6, and 9 only.

[p] Samples will be collected on Cycle 3 only.

[q] Time points for samples for PK analysis will be collected as specified in Table A-5.

[r] A baseline contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis in addition to an FDG-PET scan for lymphoma patients must be acquired at screening. 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. Contrast-enhanced CT or MRI and FDG-PET (for lymphoma patients) should be performed every 8 weeks (±7 days) from C1D1 for the first 6 months and every 12 weeks (±7 days) thereafter, or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (ie, administration of TAK-981). The same imaging modality (contrast-enhanced CT or MRI and FDG-PET scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients as clinically indicated. See Section 9.4.1.15. Response will be determined according to RECIST v1.1 for patients with solid tumors or Lugano criteria for patients with lymphoma.

[s] At EOT, tumor assessments will be performed only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

[t] Patients in PFS follow-up (patients who discontinued treatment for any reason other than disease progression or new anticancer treatment), disease assessment will be performed every 12 weeks (±7 days), or more frequently if clinically indicated. See Section 9.4.1.15.

[u] Screening and on-treatment paired tumor biopsies are mandatory for patients enrolled during Phase 2 Stage 1 of the study and are encouraged from (but optional for) patients enrolled during Phase 2 stage 2 of the study. The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of study drug. On-treatment tumor biopsies should be collected on C2D8 (+7 days). Refer to Section 9.4.1.16.3 for details.

[v] Banked formalin-fixed paraffin-embedded tumor tissue or unstained slides of the tumor tissue. Please refer to Section 9.4.1.16.3 for details.

[w] TAK-981 will be administered in a 21-day cycle at the dose level and dosing schedule determined at the end of Phase 1. TAK-981 will be administered on Day 1; Days 1 and 8; or Days 1, 4, 8, and 11. 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. At least 72 hours should elapse between consecutive doses of TAK-981. For further details on TAK-981 administration, refer to Section 8.1.

Table A-5 Phase 2 Cancer Treatment Expansion Cohorts: Plasma PK Sampling Schedule

		Cycle 1		Cycle 2	
	Day 1	**Day 4**	**Day 8**	**Day 1**	**Day 8**
	PK (Plasma)	**PK (Plasma)**	**PK (Plasma)**	**PK (Plasma)**	**PK (Plasma)**
Before TAK-981 dose (within 1 h before the start of infusion)	X	X	X	X	X
End of TAK-981 infusion (±10 min)	X	X [a]	X	X	X
2 h after end of TAK-981 infusion (±30 min)			X	X	X
4 h after end of TAK-981 infusion (±30 min)	X		X		

PK: pharmacokinetic.

[a] If TAK-981–related cumulative toxicity, PK, or pharmacodynamics support the modification of TAK-981 dosing from Days 1, 4, 8, and 11 every 21 days to Day 1, or Day 1 and Day 8, or Day 1, Day 8, and Day 15 of every 21-day dosing cycle, this test or procedure should not be performed.

Table A-6 Phase 2 Cancer Treatment Expansion Cohorts: Biomarker Sample Collection

	Screening	C1D1			C1D8			C2D1	C2D8	C3D1, C6D1, C9D1	C3D8, C6D8, C9D8
		Predose	8 h post-EOI (±30 min)	24 h post-EOI (±60 min)	Predose	8 h post-EOI (±30 min)	24 h post-EOI (±60 min)	Predose	+7 days	Predose	Predose
Archival (banked) tumor tissue sample	X										
Fresh tumor tissue biopsy sample [a]	X								X		
[redacted]											

CxDx: Cycle x, Day x; EOI: end of infusion; [redacted]. "Post-EOI" refers to end of TAK-981 infusion.

[a] The screening/pretreatment tumor tissue biopsy should be performed at least 2 days after the last dose of any prior antineoplastic therapy and within 14 days before the first dose of the drug. Screening and on-treatment biopsies are compulsory for patients enrolled during Phase 2 stage 1 portion of the study. For all other patients, paired fresh tumor biopsies are encouraged but optional. The on-treatment tumor biopsy will be collected on C2D8 (+7 days). The accessible lesion biopsy should not have been previously designated as the only target lesion for measurable disease or being located in a previously irradiated area. Ideally, the same lesion should be biopsied before treatment and during treatment whenever possible. Collection timing of the on-treatment biopsy may be changed should data collected during the study would be supportive of such a change. A decision to stop tumor biopsies collection may take place should sufficient tumor-related data be generated.

[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 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 that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB 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, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
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, US, and Japan), including the following:

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

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 et al, 1982 [64].

ECOG: Eastern Cooperative Oncology Group.

Appendix E Drugs that Interact With the CYP3A Family of CYPs

Drugs listed in the table that are strong or moderate inducers or inhibitors of the CYP3A family of CYPs are 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 carbamazepine enzalutamide mitotane phenytoin rifampin St John's wort	boceprevir cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir telithromycin troleandomycin voriconazole clarithromycin idelalisib nefazodone nelfinavir

Drugs Inducing or Inhibiting CYP3A Metabolism That Are Prohibited Concomitant Medications With TAK-981	
Moderate CYP3A Inducers [a]	**Moderate CYP3A Inhibitors** [b]
bosentan efavirenz etravirine phenobarbital primidone	aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil

CYP: cytochrome P450.

[a] Reference:
fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (accessed 13 October 2021).

[b] Reference:
fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (accessed 13 October 2021).

Appendix F Examples of Clinical Inhibitors of P-gp

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

Transporter	Gene	Inhibitor
P-gp	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/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2 (accessed 13 October 2021)..

P-gp: P-glycoprotein.

Appendix G BLRM (for Phase 1 Dose Escalation and Phase 2 Cancer Expansion Cohorts)

It is anticipated that up to approximately 132 patients will be enrolled including up to approximately 70 patients in Phase 1 (dose escalation) and up to approximately 132 patients in the 6 expansion cohorts in Phase 2 to evaluate the efficacy in patients with select solid tumors and lymphoma.

An adaptive BLRM with overdose control will be used to guide dose escalation. BLRM guided by Escalation With Overdose with Control principle [65,66] 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 (0.01,0.02, 0.05, 0.08, 0.1, 0.12, 0.2, 0.25, 0.3, and 0.6) at provisional dose levels (3, 6, 10, 15, 25, 40, 60, 90, 120, and 160 mg), as described in Neuenschwander 2008 [65].

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 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 8.2.2.

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 the following table.

Dose Escalation Simulation Study of the Probability of Dose-Limiting Toxicity

	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 following table shows the operating characteristic results. 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 35.3% and 50.3%, respectively. In Scenario 1, the average number of patients required is approximately 32 with 1.7 DLTs expected on average. The true DLT rates in Scenarios 2 increase faster than Scenario 1 but are still all below 0.33, and the BLRM has 74.8% chance of successfully recommending target dose levels. The average number of patients required is approximately 31, with approximately 3.1 DLTs expected on average. In Scenario 3, there is 6.2% chance of recommending a lower dose as MTD, 90.2% chance of successfully recommending target dose levels. The average number of patients required is approximately 28, with approximately 4.6 DLTs expected on average. In Scenario 4, with further faster increase of DLT rate over doses, there is a 73.2% probability of recommending target dose levels, whereas the probability of recommending toxic doses is 11.8%. The average number of patients required is approximately 23 with 5.3 DLTs expected on average. In Scenario 5, there is 48.3% chance of claiming the target doses as MTD, 10.8% chance of recommending a toxic dose, and approximately 40.9% chance of claiming all doses are toxic. Most of the patients (approximately 72.0%) do not receive doses above the MTD dose. The average number of patients required is approximately 13 with 4.4 DLTs expected on average. In Scenario 6 when all doses are toxic, there is a 91.6% chance of successfully claiming all doses are toxic. The average number of patients required is approximately 6 and 3 DLTs are expected on average.

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	32.0	1.7
2	25.2%	74.8%	NA	72.5%	27.5%	NA	31.0	3.1
3	6.2%	90.2%	3.6%	45.5%	51.2%	3.7%	27.9	4.6
4 (a)	11.8%	73.2%	11.8%	33.1%	53.3%	13.6%	22.9	5.3
5 (b)	NA	48.3%	10.8%	NA	72.0%	28.0%	13.4	4.4
6 (c)	NA	NA	8.4%	NA	NA	100%	6.1	3.1

BLRM: Bayesian logistic regression modeling; DLT: dose-limiting toxicity; MTD: maximum tolerated dose.
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 3.2% to claim all doses are toxic.

[b] Probability of 40.9% to claim all doses are toxic.

[c] Probability of 91.6% to claim all doses are toxic.

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 the following table to illustrate how BLRM guides dose escalation.

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	
	10	3	0	15
4	3	3	0	
	6	3	1	
	10	3	0	
	15	3	2	10
5	3	3	0	
	6	3	1	
	10	6	2	
	15	3	2	6
6	3	3	0	
	6	6	1	
	10	6	2	
	15	3	2	6 mg is claimed as the MTD

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.

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

The use of the following drugs known to prolong QTc interval are prohibited during Phase 1. In Phase 2, patients taking such medications need not to discontinue if their baseline QTcF <480 msec.

Drug Class	Examples of Drugs that Increase the 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 (Caprelsaa)
Antidepressant	citalopram (Celexa)
Antiemetic	domperidone (Motilium) droperidol (Inapsine)
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)
GI stimulant/heartburn	cisapride (Propulsid)
Opiate agonist	levomethadyl (Orlaam) methadone (Dolophine, Methadose)

Appendix I Protocol History

Date	Amendment Number	Amendment Type	Region
09 November 2021	Amendment 7	Substantial	Global
14 December 2020	Amendment 6	Substantial	Global
28 August 2020	Amendment 5	Substantial	Global
10 April 2020	Amendment 4	Substantial	United States and Canada
31 March 2020	Amendment 3	Substantial	United States and Canada
26 March 2019	Amendment 2	Substantial	United States and Canada
10 July 2018	Amendment 1	Nonsubstantial	United States and Canada
07 May 2018	Initial protocol	Not applicable	United States and Canada

Rationale for Amendment 6

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

The primary reason for this amendment was to address the United States (US) Food and Drug Administration (FDA) request to remove coronavirus disease 2019 (COVID-19) expansion cohort.

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

Protocol Amendment 6		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
The study title on the title page Section 2.0 STUDY SUMMARY	Removed details of COVID-19 population from study title.	Change made to incorporate FDA feedback to remove COVID-19 expansion.
Section 2.0 STUDY SUMMARY	Change in number of sites.	The study will be conducted in approximately 60 sites globally.
Section 4.1 Immunotherapy in Cancer Section 4.2 Background Section 4.2.1 Nonclinical Pharmacology Section 4.2.4 Preliminary Clinical Experience Section 4.3 Rationale for the Proposed Study	Updated clinical and nonclinical data.	Section updated to align with data provided in latest Investigator Brochure (IB) (Edition 3).

Protocol Amendment 6		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 4.3 Rationale for the Proposed Study	Removed rationale for use of TAK-981 in patients with locally advanced or metastatic solid tumors or relapsed/refractory hematologic malignancies with COVID-19. Also removed complete subsection on rationale for COVID-19 expansion.	Change made to incorporate FDA feedback to remove COVID-19 expansion.
Section 2.0 STUDY SUMMARY Section 4.3.1 Rationale for the Starting Dose and Schedule Section 6.1.1 Phase 1 Dose Escalation Appendix A SOE	Added less intensive TAK-981 dosing schedule of Day 1, Day 8, and Day 15 in 21-day cycle.	To provide more clarity on potential change in cycles in patients with clinical benefit.
Section 2.0 STUDY SUMMARY Section 5.1 Objectives Section 5.2 Endpoints Section 6.1 Overview of Study Design Section 6.2 Number of Patients Section 6.4 Duration of Study Section 7.0 STUDY POPULATION Section 8.0 STUDY DRUG Section 9.4 Study Procedures Section 11.0 STUDY-SPECIFIC COMMITTEES Section 13.0 STATISTICAL METHODS Section 16.0 REFERENCES Appendix A SOE	Removed COVID-19 expansion details from all the sections of the protocol, references, and appendices.	Change made to incorporate FDA feedback to remove COVID-19 expansion.
Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 6.2 Number of Patients	Increased number of subjects in dose-escalation phase.	Change incorporated to facilitate testing of alternative dosing schedules in dose escalation phase.
Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design	For Phase 2 cancer treatment expansion, revised population for Cohort E (relapsed/refractory DLBCL that have not received prior cellular therapy).	To align with the pre-existing inclusion criterion.

Protocol Amendment 6		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.1 Inclusion Criteria Section 8.5 Precautions and Restrictions Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Changed the contraceptive requirement from 90 days to 120 days.	Change made to align with Takeda standard.
Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Correction done in patient population cohort B- changed from "prior 2 systemic lines" to "prior 1 systemic line"	Change to align the Summary Section with Protocol Section 7.
Section 9.4.1.16.5 Pharmacodynamic Measurements Appendix A SOE	Added elaborate details on each type of pharmacodynamic measurement in respective section.	Change incorporated for better clarity on pharmacodynamic measurements.
Appendix A SOE	Updated time point for adduct/conjugates to 1 h ±20 min post end of infusion (EOI) (instead of 2 h). Switched columns of 1 h and 2 h post EOI.	A typo was corrected to ensure that sumo/adduct blood sample collection on Cycle 1 Day 8 will be at 1 h post EOI and not at 2 h post EOI. Switched columns for chronological accuracy.
Appendix A SOE	[redacted]	Correction of a typo.

Rationale for Changes in Amendment 5

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

The primary reason for this amendment was to incorporate a Phase 2 portion to assess the preliminary efficacy of TAK-981 in select tumor types and indications 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 purpose only.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
The study title on the title page Section 2.0: STUDY SUMMARY	This study will now be conducted in 2 phases (Phase 1 and Phase 2) instead of Phase 1 only.	To incorporate a Phase 2 portion to assess the preliminary efficacy of TAK-981 in select tumor types and indications in the clinical trial design.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Title page Section 2.0: STUDY SUMMARY	Addition of EudraCT number.	EudraCT number is obtained as a part of plan to expand the study conduct globally.
Section 1.2 Approval	Changed the name of 1 signatory.	To update the document with the current Takeda function that is accountable for the study protocol.
Section 2.0: STUDY SUMMARY	Change in number of sites.	The study will be conducted in approximately 50 sites globally.
Section 4.1: Immunotherapy in Cancer	Added background information about immunotherapy in cancer, solid tumors (lung cancer, cervical cancer, colorectal cancer), and non-Hodgkin lymphoma (NHL) (indolent NHL, aggressive NHL).	To provide background information on the incidence, therapeutic landscape, and medical need of the tumor histologies and indications selected for the Phase 2 portion of the study.
Section 4.3 Rationale for the Proposed Study	Restructured text to create a section for a rationale for the proposed patient population.	To provide a rationale for the proposed patient population.
Section 4.3.1 Rationale for the Starting Dose and Schedule	Clarified that patients with clinical benefits can be changed to less frequent dosing schedule after Cycle 9 upon discussion and agreement between the investigator and sponsor.	To provide more clarity on potential change in cycles in patients with clinical benefit.
Section 4.4 Potential Risks and Benefits	Added details about ongoing trials in which TAK-981 is being investigated.	To provide current data available.
Section 4.4.1.1 Lymphoid and Hematopoietic Effects	Modified language regarding potential lymphoid and hematopoietic effects based on nonclinical studies.	To align the risk of transient lymphopenia with the modifications applied in Section 7 and Section 8.
Section 4.4.1.2 Effects in Renal Pelvis	Modified language regarding potential renal pelvis effects based on nonclinical studies.	To include a more flexible hydration requirement for patients based on principal investigator guidance and experience.
Section 4.4.1.3 IRRs and Potential for CRS	Modified language regarding infusion related reactions and potential for cytokine release syndrome.	To clarify that these precautions are for dose escalation Phase 1.
Section 4.4.1.5 Reproductive and Development Toxicity	Added data for potential reproductive and development toxicity based on nonclinical studies.	To incorporate additional prevention of risks based on emerging preclinical data.
Section 4.4.1.6 Genotoxicity	Added data for potential genotoxicity based on nonclinical studies.	To incorporate emerging preclinical data.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0: STUDY SUMMARY Section 5.1.1 Primary Objectives	Promoted secondary objective to establish recommended Phase 2 dose (RP2D) of TAK-981 to primary objective in Phase 1 of the study.	The previous objectives described in the Phase 1b trial has been distributed among the Phase 1 and Phase 2 portions of the trial to align objectives and the study design.
Section 2.0: STUDY SUMMARY Section 5.1.1 Primary Objectives	Added primary objective to evaluate efficacy of TAK-981 in patients participating in Phase 2 of the study.	The previous objectives described in the Phase 1b trial has been distributed among the Phase 1 and Phase 2 portions of the trial to align objectives and the study design.
Section 2.0: STUDY SUMMARY Section 5.1.2 Secondary Objectives	Modified secondary objectives for Phase 1 and added secondary objectives for Phase 2 of the study.	The previous objectives described in the Phase 1b trial has been distributed among the Phase 1 and Phase 2 portions of the trial to align objectives and the study design.
Section 5.1.3 Exploratory Objectives	[redacted]	[redacted]
Section 5.1.3 Exploratory Objectives	[redacted]	[redacted]
Section 5.1.3 Exploratory Objectives	[redacted]	[redacted]
Section 2.0: STUDY SUMMARY Section 5.2 Endpoints Section 6.4.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures	Modified primary, secondary, and exploratory endpoints based on the changes in primary, secondary, and exploratory objectives.	To align endpoints with the changes in objectives.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0: STUDY SUMMARY Section 6.1 Overview of Study Design	Modified the overview of study design and study schematic to provide details of study conduct during Phase 1 (dose escalation) and Phase 2 (cancer treatment expansion cohorts) of study.	To provide an accurate overview of the new study design.
Section 2.0: STUDY SUMMARY Section 6.1.1 Phase 1 Dose Escalation	Modified language for Phase 1 dose escalation of TAK-981.	To avoid redundancy across the protocol.
Section 6.1.1 Phase 1 Dose Escalation	Modified language regarding the circumstances that may warrant enrollment hold.	To clarify language and update who will review the safety data.
Section 2.0: STUDY SUMMARY Section 6.1.2 Phase 2 Expansion in Select Cancer Indications	Added section to describe Phase 2 expansion of select indications.	To better screen the potential antitumor activity of TAK-981 [redacted]
Section 6.2 Number of Patients Section 13.4.1 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts Appendix G Bayesian Logistic Regression Model (for Phase 1 Dose Escalation and Phase 2 Cancer Expansion Cohorts)	Increased the sample size of the study.	This change was made to power each of the 6 Phase 2 cohorts with the minimum number of patients (Phase 2 stage 1) required to reject futility and proceed to expanding enrollment in the case of compelling overall response rate (ORR).
Section 6.3 Patient Replacement	Modified the language to clarify that patients enrolled in Phase 2 will not be replaced.	To clarify that patients in the Phase 2 portion will not be replaced.
Section 6.4.1 Duration of an Individual Patient's Study Participation	Modified the language regarding duration of an individual patient's study participation.	To avoid redundancy across the protocol.
Section 6.4.2 End of Study/Study Completion Definition and Planned Reporting Section 6.4.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures Section 6.4.4 Total Study Duration	Increased study duration from 24 to 36 months to now up to 48 months and increased maximum time frame up to 48 months for primary and secondary endpoints for disclosures.	To account for potential slower recruitment of patients with select tumor types and indications.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Modified inclusion criterion to include patient population with cytologically confirmed advanced or metastatic solid tumors that have no standard therapeutic option with a proven clinical benefit, are intolerant, or have refused them.	To allow the enrollment of patients with metastatic solid tumors diagnosed by cytology.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Added inclusion criteria on patient population to be included in Phase 2 cohorts.	To clarify the different tumor types and indications to be enrolled during Phase 2.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Modified inclusion criterion for radiologically measurable lesions in Phase 2.	To clarify that irradiated tumor lesions can be considered measurable lesions if progressive disease has been demonstrated in that particular lesion.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Added inclusion criterion for willingness to consent to mandatory pretreatment and on-treatment biopsy in Phase 2 stage 1.	To restrict the mandatory collection of paired tumor biopsies to Phase 2 stage 1.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Added inclusion criterion for willingness to provide archival tumor tissue sample, if available, in all patients except those in coronavirus disease 2019 (COVID-19) expansion.	To confirm subject's willingness to provide archival tumor tissue sample for biomarker analysis, if available.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	For COVID-19 expansion, modified the inclusion criterion to increase the peripheral capillary oxygen saturation requirement to >93% on room air.	Change is made to follow Food and Drug Administration's (FDA's) definition of COVID-19 infected patients with moderate disease.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	For COVID-19 expansion, modified the inclusion criterion to include patients with moderate disease (National Early Warning Score ≤6).	Changed term "moderately severe" to "moderate" to clarify that only patients with moderate COVID-19 disease will be eligible for enrollment in COVID-19 expansion.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Lowered the lower limit of absolute neutrophil count requirement (≥1.0 × 109/L) for inclusion in study and modified language for the hemoglobin and platelet count requirements.	To comply with American Society of Clinical Oncology guidelines published in the Journal Clinical of Oncology 2017 and the recommendations from principal investigators.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Deleted inclusion criterion related to absolute lymphocyte count.	This change was made in agreement with principal investigators, who concurred that low lymphocyte counts did not appear to correlate with severe clinical outcomes in multiple examples of immunomodulatory and chemoradiotherapeutic regimens. In addition, the baseline lymphopenia in lymphoma patients and patients with solid tumors who progressed to multiple lines of therapies would preclude the eligibility of this patient population for the study.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Modified inclusion criterion recovery from all toxic effects of previous therapy.	To allow the enrollment of patients with lymphoma and Grade 2 thrombocytopenia to comply with the American Society of Clinical Oncology guidelines regarding eligibility criteria in clinical trials as described in the Journal of Clinical Oncology, October 2017, as well as per the recommendation of principal investigators.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Deleted inclusion criterion regarding screening and postdose tumor biopsies.	To avoid redundancy with other exclusion criteria.
Section 2.0: STUDY SUMMARY Section 7.1 Inclusion Criteria	Clarified that use of low-dose steroids (oral prednisone or equivalent ≤20 mg per day) within 14 days before first dose of the study drug is allowed.	To homogenize allowed doses across the TAK-981 protocols.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified the exclusion criterion by deleting language on recovering from previous treatment toxicity and adding exceptions.	Text was deleted to avoid repetition since it is also mentioned in inclusion criterion; exceptions were added to align this exclusion criterion across TAK-981 protocols.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified the exclusion criterion by clarifying patients who have not recovered to Grade 1 or baseline after extended field radiotherapy are excluded.	To avoid redundancy across the study protocol.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria Section 8.4.2 Excluded Concomitant Medications and Procedures for COVID-19 Expansion Section 8.5 Permitted Concomitant Medications and Procedures Section 9.4.2.10.1 SOC for COVID-19 Appendix A SOE	Removed the allowance of hydroxychloroquine and chloroquine use in COVID-19 expansion.	Change is made to follow FDA's guidance for treatment of COVID-19 infected patients.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified the exclusion criterion regarding uncontrolled hypertension.	To clarify the type of hypertension in this exclusion criterion.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified the exclusion criterion by replacing "baseline prolongation of the QTc interval" with "baseline prolongation of the QTcF interval."	To further clarify that corrected QT interval must be calculated with Fridericia method.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Added/modified exclusion criteria to exclude patients with history of autoimmune disease and those with immune-related adverse events (AEs), noninfectious pneumonitis, or active noninfectious pneumonitis.	To adapt the exclusion criteria to the relevant TAK-981–mediated toxicities observed during trial conduct and align with the TAK-981 program protocols.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified exclusion criterion from "active infection" to "significant active infection."	To further clarify the exclusion criterion.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria Section 8.3.1 Excluded Concomitant Medications and Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts	Added that the exclusion criterion regarding use of drugs known to prolong QTc interval was for Phase 1 only.	To clarify that the restriction applies to Phase 1 only.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Added exclusion criterion for secondary malignancy within previous 3 years, with exceptions to certain types of cancers.	To state that with some exceptions, patients with second malignancies are not eligible.
Section 2.0: STUDY SUMMARY Section 7.2 Exclusion Criteria	Added exclusion criterion for prior allogeneic tissue and solid organ transplant.	To align the exclusion criteria across all the TAK-981 study protocols.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.0 STUDY DRUG, Section 8.1 Study Drug Administration Section 8.2 Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts	Elaborated details on TAK-981 administration in Phase 1 and Phase 2 and removed redundant language.	To provide further clarification of TAK-981 administration requirements during Phase 1 and Phase 2 and to avoid redundancy.
Section 8.2.1 Definitions of DLT for Dose Escalation	Modified dose-limiting toxicity (DLT) definitions.	To reflect the consensus of the principal investigators in this regard, as baseline lymphocyte counts are significantly variable, intermittent lymphocytopenia lacks clinical significance, and baseline lymphocytopenia observed in multiple lymphoma and solid tumor patients may be aggravated by procedures and conditions other than treatment with study drug. In this study, prophylaxis for opportunistic infections is initiated as per investigator discretion.
Section 8.2.2 Dose Escalation Rules	Clarified dose escalation rules.	To clarify that the 3 + 3 design rules apply to cohort 1 only; the number of patients in each cohort from cohort 2 and above is approximately 3. Also, esthetic modifications have been applied to avoid redundancy.
Section 8.2.4.1.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle	Modified platelet count criterion and deleted lymphocyte count as one of the criteria for beginning or delaying a subsequent treatment cycle.	To align the criteria for beginning a new cycle with the baseline hematologic Grade 1 or Grade 2 alterations allowed in Section 7.
Section 8.2.4.1.3 Criteria for Dose Interruption, Dose Reduction, and Discontinuation	Deleted language regarding acute toxicity in the criteria for dose interruption, dose reduction, and discontinuation.	To avoid overexplaining.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.2.4.1.3 Criteria for Dose Interruption, Dose Reduction, and Discontinuation	Deleted lymphocytopenia as a criterion for dose adjustments for hematologic toxicities.	To reflect the consensus of the principal investigators in this regard, as intermittent lymphopenia lacks clinical significance or value as a potential pharmacodynamic biomarker, and baseline lymphocytopenia is observed in multiple lymphoma and solid tumor patients; as a mitigation of risk, prophylaxis for opportunistic infections is initiated as per investigator discretion.
Section 8.4.1 Excluded Concomitant Medications and Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts	Modified definition of a short course of concomitant corticosteroids from <48 hours to <96 hours.	To allow a more prolonged course of steroids in alignment with current guidance on the approach to certain clinical conditions.
Section 8.4.1 Excluded Concomitant Medications and Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts	Modified language regarding prophylactic use of myeloid growth factors.	To further clarify that the initiation of primary prophylaxis of cytopenia with myeloid growth factors is not allowed during Cycle 1.
Section 8.4.1 Excluded Concomitant Medications and Procedures for Phase 1 Dose Escalation and Phase 2 Cancer Treatment Expansion Cohorts	Added immunization with live viral vaccines as one of the excluded concomitant medications and procedures during the study.	To align prohibited medications across TAK-981 study protocols.
Section 8.5 Permitted Concomitant Medications and Procedures	Included receptor activator of nuclear factor kappa-B ligand inhibitors as a permitted concomitant medication.	To align across TAK-981 protocols.
Section 8.5 Permitted Concomitant Medications and Procedures	Added language clarifying that additional concomitant medications and procedures are permitted during the study to prevent and actively manage AEs unless specifically prohibited in the protocol.	To further clarify the permitted concomitant medications.
Section 8.7.5 Lymphopenia and Opportunistic Infection Prophylaxis	Changed the follow-up for lymphopenia and opportunistic infection prophylaxis from [redacted] to "CD4/8 counts."	To clarify the type of follow-up that will help investigators in making clinical decisions about the risk of immunosuppression.
Section 8.7.7 CRS	Modified language regarding cytokine release syndrome.	To provide further information on signs and symptoms of cytokine release syndrome.

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Section 9.4 Study Procedures	Modified general language regarding study procedures and deleted language regarding image tests.	To clarify language and to avoid redundancy since this is described in the schedule of events (SOE) table.
Section 9.4.1.3 Medical History	Clarified that any available pathology/cytogenetic/mutational and tumor genomic information should be reported in the electronic case report form (eCRF).	To further clarify collected information must be reported in eCRF.
Section 9.4.1.5 Patient Height and Weight	Modified language regarding patient height and weight.	To avoid conflicts with the SOE table.
Section 9.4.1.8 Pregnancy Test Appendix A SOE	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 visit.	To clarify that pregnancy tests are required on Day 1 of each cycle in women with childbearing potential.
Section 9.4.1.12 Post-Treatment Follow-up Section 9.4.2.1.13 Posttreatment Follow-up	Modified language regarding posttreatment follow-up assessments and separated the sections for posttreatment follow-up for Phase 1 dose escalation and Phase 2 cancer treatment expansion, and COVID-19 expansion.	To avoid redundancy within Section 9 and to provide separated sections specific for each cohort.
Section 9.4.1.13 Cardiac Monitoring	Modified language regarding 12-lead electrocardiograms (ECGs), left ventricular ejection fraction and [redacted].	To avoid conflicts with the SOE table and to clarify that [redacted] will not be collected during Phase 2.
Section 9.4.1.14.1 Chemistry, Hematology, Coagulation, and Urinalysis	Modified language regarding chemistry, hematology, coagulation, and urinalysis.	To homogenize the window period for sample collection.
Section 9.4.1.15 Disease Assessment Section 13.2.3 Efficacy Analysis	Removed Response Evaluation Criteria in Lymphoma (RECIL) throughout the protocol and added Lugano criteria for lymphoma response to assess disease response and progression.	To align the criteria to evaluate response in lymphoma patients across TAK-981 studies.
Section 9.4.1.16 Biomarker, Pharmacodynamic, and PK Samples	Added detailed procedure for tumor biopsies, banked tumor, and fresh paired tumor biopsy.	To provide flexible window periods for the collection of paired tumor biopsies and to align the biopsy procedure with the requirements requested by FDA in the Study TAK-981-1501 protocol.

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Section 9.4.1.16.5 Pharmacodynamic Measurements Table 9.d Primary Specimen Collection Section 13.2.1 Analysis Sets	[redacted]	To incorporate an additional measure of response or TAK-981 resistance in Phase 2 of the study.
Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Modified language regarding discontinuation of treatment with study drug, including adding occurrence of a DLT.	To clarify the reasons for study drug discontinuation and to avoid redundancy.
Section 10.1.2 AE Definition	Added language that disease progression should not be reported as an AE.	To provide sites and investigators with guidance on how to report outcomes and AEs.
Section 10.1.3 SAE Definition	Added language to clarify when death or hospitalization is regarded as an serious adverse event (SAE).	To provide sites and investigators with further guidance on how to report SAEs.
Section 11.0 STUDY-SPECIFIC COMMITTEES	Modified language regarding study-specific committees.	To allow an independent assessment of the benefit-risk of treatment with TAK-981 in patients enrolled during Phase 2 stage 2.
Section 13.2.1 Analysis Sets	Modified language regarding the pharmacodynamic analysis sets.	To homogenize terminology regarding postdose or on-treatment tumor biopsies across the study protocol.
Section 13.2.3 Efficacy Analysis	Updated efficacy analysis section.	To align the different efficacy analyses with the objectives described in each phase of the study protocol.
Section 13.2.4 PK Analysis	Added language to the pharmacokinetic analysis section regarding Phase 1 and Phase 2.	To align the different analyses with the objectives described in each phase of the study protocol.
16.0 REFERENCES	Updated references.	To reflect added and deleted citations in the amended text.
Appendix A SOE	Added separate SOE tables for Phase 2 and modified SOE tables to account for differences between Phase 1 and Phase 2 assessments.	To provide clear guidance on the study procedures and tests to be performed in each portion of the Phase 1/2 study.
Appendix H Examples of QTc Interval Prolonging Agents (Phase 1 Only)	Modified language in Appendix H Examples of QTc Interval Prolonging Agents.	To clarify that the prohibition on QTc-prolonging agents applies to Phase 1, when the QT analysis is performed.

Protocol Amendment 5		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix E Drugs that Interact with the CYP3A Family of Cytochromes P450	Updated lists of drugs that are strong or moderate inducers or inhibitors of the CYP3A family of cytochrome P450.	To align with FDA's most current list of strong or moderate inducers or inhibitors of the CYP3A.

Rationale for Amendment 04

This document describes the changes to the protocol incorporating Amendment 04. The primary reason for this amendment was to incorporate changes requested by United States Food and Drug Administration (FDA) during the review of protocol incorporating Amendment 03 that intended to explore potential of TAK-981 to control severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cancer by modulating Type I interferon response.

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 J [of Protocol Amendment 4].

Changes in Amendment 04

1. Amended the title of the study to accurately describe the patient population of this study.
2. Added a section on rationale for coronavirus disease 2019 (COVID-19) expansion design.
3. Amended the study design in the COVID-19 expansion to include safety lead-in and randomized COVID-19 proof of concept cohorts.
4. Added figure for overall TAK-981-1002 study design.
5. Interchanged the text under potential risks and benefits and preliminary clinical experience.
6. Added details on inclusion of Independent Data Monitoring Committee.
7. Replaced term "Phase 1" with "dose escalation and cancer treatment expansion" throughout protocol for more clarity.
8. Modified primary objective for COVID-19 expansion to clarify that change in SARS-CoV-2 viral load will be assessed within 8 days of TAK-981 administration.
9. Modified primary endpoint for COVID-19 expansion.
10. Clarified that time to discharge or the maintenance of a National Early Warning Score of ≤3 for 24 hours, whichever occurs first, is the key secondary endpoint and added another new key secondary endpoint.
11. Added duration of supplemental oxygen requirement as a secondary endpoint.

[redacted]

13. Amended study stopping rules in the COVID-19 expansion.
14. Amended number of patients to be enrolled in COVID-19 expansion.
15. Modified inclusion criteria for evaluation of TAK-981 in SARS-CoV-2 patients with locally advanced or metastatic solid tumors or relapsed/refractory hematologic malignancies that have COVID-19.
16. Modified exclusion criteria for COVID-19 expansion to exclude patients requiring use of drugs known to prolong corrected QT interval with specific exceptions.
17. Added section on dose modification guidelines for COVID-19 expansion.
18. Added section on excluded concomitant medications and procedures for COVID-19 expansion.
19. Amended the list of permitted concomitant medications and procedures for COVID-19 expansion.
20. Clarified throughout the protocol that cytokine release syndrome will be graded according to ASTCT Concensus Grading of CRS, added table for CRS management recommendations, and amended TAK-981 dose modification.
21. Amended treatment group assignments section to add details on randomization.
22. Added details on standard of care for COVID-19.
23. Clarified that nasopharyngeal and oropharyngeal specimes will be used to test SARS-CoV-2 viral load and nasopharyngeal swab will be collected from both or same nostril(s) for each timepoint.
24. Added details on adverse events of special interest.
25. Added a separate statistical methods section for COVID-19 expansion.
26. Added details on determination of sample size for COVID-19 expansion.

Rationale for Amendment 03

This document describes the changes to the protocol incorporating Amendment 03. The primary reason for this amendment was to explore the potential of TAK-981 to control severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection in patients with cancer by modulating Type I interferon response. The amendment also addresses study conduct during the Coroanvirus Disease 2019 (COVID-19) pandemic.

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 J [of Protocol Amendment 3].

Changes in Amendment 03

1. Changed the study title to replace "Lymphoma" with "Hematologic Malignancies"
2. Changed the names of 2 signatories.
3. Modified nonclinical pharmacology text to reflect current data available.
4. Added text for nonclinical toxicology and potential effects based on nonclinical studies by addition of details on reproductive and development toxicity and genotoxicity.
5. Modified potential risks and benefits section to reflect current data available from TAK-981 administration in humans in 2 ongoing clinical trials.
6. Added details about safety monitoring committee and its role in the study.

To incorporate the COVID-19 expansion, following additions/changes were done:

7. Added details on evaluation of TAK-981 effect in patients with solid tumors or hematologic malignancies that have SARS-CoV-2 infection.
8. Added a sub-section describing details on dose level and schedule in COVID-19 expansion.
9. Added a sub-section describing rationale for conducting COVID-19 expansion.
10. Added a sub-section describing rationale for COVID-19 specific sample collection.
11. Added primary and secondary objectives for COVID-19 expansion.
12. [redacted]
13. Added primary and secondary endpoints for COVID-19 expansion.
14. Added a sub-section under overview of study design for COVID-19 expansion.
15. Added details on number of patients to be enrolled in COVID-19 expansion.
16. Added details about duration of individual patient's participation in COVID-19 expansion cohort.
17. Added definition of end of study/study completion and details of reporting for COVID-19 expansion cohort.
18. Added disclosures information (endpoint, definition, and time frame) for primary and secondary endpoints in COVID-19 expansion.
19. Added details about total duration of COVID-19 expansion cohort.
20. Clarified that post study access will not be applicable for patients enrolled in COVID-19 expansion.

21. Modified inclusion criteria for patient enrollment in the study by adding specific criteria for COVID-19 expansion.
22. Modified exclusion criteria for patient enrollment in the study by adding specific criteria for COVID-19 expansion.
23. Added details for TAK-981 administration in COVID-19 expansion.
24. Modified text for hydration and vital signs during C1D1 administration.
25. Clarified that dose adjustments criteria under lymphocytopenia are applicable for patients enrolled in dose escalation or cancer treatment expansions only.
26. Restructured list of excluded concomitant medications and procedures.
27. Added list of concomitant medications and procedures permitted in COVID-19 expansion.
28. Added a separate sub-section elaborating on all study procedures for COVID-19 expansion cohort.
29. Rearranged criteria for completion of study to distinguish situations for overall study and those for dose escalation and cancer treatment cohort only.
30. Rearranged criteria for discontinuation of treatment with TAK-981 to distinguish discontinuation criteria for overall study and those for dose escalation and cancer treatment cohort only.
31. Added details on posttreatment follow-up assessments for patients in COVID-19 expansion cohort.
32. Modified definition for SAE to include criteria for COVID-19 patients.
33. Clarified that a separate statistical analysis plan (SAP) will prepared for COVID-19 expansion.
34. Added details about COVID-19 response evaluable analysis set.
35. Added details about antiviral efficacy analysis for COVID-19 expansion.
36. Added language for remote monitoring visits for COVID-19 expansion.
37. Added sample size calculation for COVID-19 expansion cohort.
38. Added 2 tables (Schedule of events and PK and biomarker sample collection) for COVID-19 expansion in Appendix A.
39. Added Appendix F for National Early Warning Score.
40. Added footnotes in SOE tables to incorporate language for documentation of reasons for missed assessments or procedures.

Rationale for Amendment 2

This document describes the changes to the protocol incorporating Amendment 02. The primary reasons for this amendment are to modify the lymphopenia limit inclusion criteria and to clarify how and when various tests and procedures should be performed.

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

Changes in Amendment 02

1. Added that the dosing schedule may be modified to a less intense one without a protocol amendment if TAK-981–related cumulative toxicity is observed or if supported by emerging pharmacokinetic (PK)/pharmacodynamic data.
2. Increased the estimated number of sites to be used in the study.
3. Removed language stating that the screening biopsy could be replaced by an archival biopsy.
4. Removed examples of blood pressure levels from exclusion criterion #5.
5. Changed the length of time that on Cycle 1, Day 1 (C1D1), patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours before collection of the predose electrocardiograms (ECGs) until after collection of the 1-hour postinfusion ECGs and that a low calorie and low sodium light meal is permitted immediately after the 1-hour post-infusion ECG has been collected.
6. Ensured that the primary endpoints in the protocol and study summary matched.
7. Updated background information on how TAK-981 affects the small ubiquitin-like modifier (SUMO)ylation process based on more recent nonclinical research.
8. Added 3 safety primary endpoints to the list to be reported to Disclosures.
9. Among the inclusion criteria that define adequate bone marrow reserve and renal and hepatic function in the inclusion criteria, modified absolute lymphocyte thresholds and include a minimum requirement of CD4 lymphocytes for patients with absolute lymphopenia.
10. Modified the lymphocyte count criterion that patients must meet to begin a new cycle of treatment.
11. Added that a dose delay of up to 4 days may occur under certain conditions and that 72 hours should elapse between consecutive doses of TAK-981.
12. Clarified that Grade 3 fatigue will not be considered a dose-limiting toxicity (DLT) if it lasts fewer than 7 days.
13. Added that Grade 3 cytokine release syndrome will not be considered a DLT.
14. Added that if TAK-981 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 schedule of events (SOE).
15. Clarified how to adjust dose if the patient experiences Grade 4 neutropenia.
16. Clarified how to adjust dose if the patient experiences Grade 4 thrombocytopenia.
17. Clarified how to treat lymphopenia.
18. Added a 7-day window for image tests.

[redacted]

21. Added that if transmission of a pregnancy report is not feasible, then a facsimile of the completed Takeda paper-based pregnancy form will be sent.
22. Clarified definitions of various pharmacodynamic analysis datasets.
23. Made multiple changes in SOE and footnotes to match new protocol sample collection requirements, and to provide clarifications or correct typos.
24. Added language stating that a decision to stop the collection of skin punch biopsies may take place should sufficient data related to target engagement and small ubiquitin-like modifier 2 (SUMO2)/ small ubiquitin-like modifier 3 (SUMO3) inhibition be generated.
25. Added language stating that a decision to omit the collection of the 8-hour post–end-of-infusion blood sample for flow cytometry may occur should sufficient data related to target engagement and SUMO2/3 inhibition in peripheral blood in earlier collection time points be generated.
26. Added grapefruit to list of prohibited concomitant medications.
27. Added "lack of benefit" and "clinical progression" to the list of reasons that treatment with study drug may be discontinued.
28. Added that the same lesion should be biopsied before treatment and on treatment whenever possible.
29. Added that 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.
30. Modified the amount of fluid intake from 2 liters to 1 liter in the 4 hours after the infusion, and clarified that if the patient cannot drink this amount of fluid, extra IV fluid supplementation should be considered at the investigator's discretion.
31. Day 11 PK samples have been moved to Day 8.
32. Day 11 blood samples have been moved to Day 8.
33. Removed stipulation that vital signs should be assessed every 30 minutes during the 2 hours following infusions.
34. Modified the number of patients to be enrolled in cohorts during the dose escalation phase.

Rationale for Amendment 1

This document describes the changes to the protocol incorporating Amendment 01. The primary reason for this amendment is to incorporate changes requested by the United States (US) Food and Drug Adminsitration during review of the protocol.

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

Changes in Amendment 01

1. Added to the study design that for a certain dose level (DL) to be considered as a potential recommended phase 2 dose (RP2D), the percentage of adverse events (AEs) meeting the dose-limiting toxicity (DLT) definition at any cycle should be <33%.
2. Added the circumstances related to the determination of an overall excess of toxicity that may warrant enrollment hold.
3. Modified an inclusion criterion to state that patients must not have a therapy with proven clinical benefit available to them to be enrolled in the study.
4. Added to an inclusion criterion that patients with low-grade lymphomas may not need to exhaust all available therapy to be enrolled in the study under certain conditions.
5. Modified an exclusion criterion exclude patients who use moderate inhibitors and inducers of cytochrome P450 (CYP) 3A4/5.
6. Modified the definition of DLT to:
   a) Clarify that the listed AEs must be clearly unrelated to TAK-981 to not be considered a DLT.
   b) Include "any Grade 5 AE".
   c) Define a maximum allowable duration for uncomplicated Grade 3 thrombocytopenia.
   d) Indicate that AEs meeting the DLT definition happening outside Cycle 1 will be taken into consideration by bayesian logistic regression modeling (BLRM) for determination of the RP2D.
7. Added clarifications to the criteria for dose interruptions and reductions.
8. Modified the general dose modification recommendations for TAK-981 nonhematologic drug-related AEs to reflect changes to criteria for dose interruptions, reductions, and discontinuation.
9. Clarified that patients who require use of strong and moderate inhibitors/inducers of CYP3A4/5 during the study should temporarily discontinue use of TAK-981.
10. Added that narrow therapeutic range P-glycoprotein (P-gp) substrates such as digoxin or dabigatran may to be used with caution, and patients requiring use of these drugs will be closely monitored.
11. Relocated the dose adjustments for hematologic toxicities table and made the levels of dose reductions more explicit.
12. Clarified what kinds of pharmacokinetic (PK) and pharmacodynamic evidence will be used to determine the RP2D.
13. Added a list of moderate CYP3A inducers and inhibitors to the appendix that describes prohibited concomitant medications with TAK-981.

14. Added that the 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.
15. Clarified in the exclusion criteria that patients should not have received treatment with anticancer treatments or investigational products within 14 days before first dose of study drug.
16. Aligned time points for multiple-gated acquisition (MUGA) scans/echocardiograms in the schedules of events (SOEs) and study procedures sections.
17. Clarified that predose/postdose tumor biopsies are optional for patients in dose escalation until there is evidence of TAK-981 pharmacodynamic effect from multiple patients or evidence of antitumor effect.
18. Added that all skin punch biopsies should be obtained from the upper back.
19. Clarified that patient enrollment will be staggered between the first and second patients during dose escalation at all DLs, and that at each DL, the second and third patients can be dosed concurrently if the first patient in the cohort has gone through the Day 4 visit without clinically significant acute toxicities.
20. Clarified that screening and postdose tumor biopsies are required from all patients in the expansion cohorts and are optional during dose escalation, but will be required from certain patients once a DL for which there is consistent evidence of TAK-981 pharmacodynamic effect has been established.
21. Added an exclusion criterion for patients who require the use of drugs known to prolong heart rate–corrected QT (QTc) interval.
22. Updated the excluded concomitant medications prohibit concomitant use of drugs known to prolong the QTc interval during the study.
23. Added examples of drugs that are known to prolong the QTc interval.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	12-Nov-2021 16:16 UTC
[redacted]	Clinical Science Approval	12-Nov-2021 19:08 UTC
[redacted]	Biostatistics Approval	12-Nov-2021 20:35 UTC
[redacted]	Clinical Approval	13-Nov-2021 16:30 UTC