Clinical Study Protocol

NCT Number: NCT04776018

Title: A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK-981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Study Number: TAK-981-1503

Document Version and Date: Amendment 2.0, 30 August 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

A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK-981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

TAK-981 in Combination With Monoclonal Antibodies in Patients With Relapsed and/or Refractory Multiple Myeloma

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

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

Study Number: TAK-981-1503

EudraCT Number: Not applicable

Compound: TAK-981

Date: 30 August 2021 **Amendment Number:** 2

Date	Amendment Number	Region
30 August 2021	Amendment 2	Global
22 December 2020	Amendment 1	Global
03 November 2020	Initial protocol	Global

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
Oncology Clinical Research
(or designee)

[redacted] PhD Date
SQS Oncology
(or designee)

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

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

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAE 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 2 Summary of Changes and Rationale

Rationale for Amendment 2

This section describes the changes to the protocol incorporating Amendment 2.

The primary reason for this amendment was to update the translational strategy for sample collection for analysis of biomarkers.

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

Protocol Amendment 2			
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	Global	Updated instances of "Phase 1" to be "Phase 1b" for this study.	Editorial update for consistency.
2	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 8.10 Precautions and Restrictions	Updated text throughout the protocol to require patients to practice effective contraception through 6 months after the last dose of study drug (instead of 120 days after the last dose of study drug or 6 months after last dose of TAK-981).	Compliance with local guidelines.
3	Section 2.0 STUDY SUMMARY Section 8.5 Dose Escalation Rules Section 13.3 Determination of Sample Size	Corrected spelling of daratumumab.	Correction.
4	Section 4.2.1 TAK-981 Section 4.4 Rationale for the Starting Dose and Schedule Section 4.5.1 Potential Effects of TAK-981	Updated clinical sections to include information from the latest TAK-981 investigator's brochure (IB) edition (Edition 4, data cutoff 28 June 2021).	Updated clinical data from the TAK-981 IB were available.
5	Section 4.5.5 Coronavirus Disease 2019 Pandemic	Added a section on benefit-risk assessment of participation in the study during the coronavirus disease 2019 (COVID-19) pandemic, indicating that the benefit/risk assessment remains favorable and that considerations for patient participation should be evaluated by the investigator on a patient by patient basis taking into consideration the current local situation, guidelines, and other recommendations.	Guidance on benefit-risk assessment for patient participation in the study during the COVID-19 pandemic.

Protocol Amendment 2			
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***
6	Section 6.5.2 End of Study/Study Completion Definition and Planned Reporting	Clarified that once TAK-981 has been discontinued, patients cannot remain on the monoclonal antibody as a single agent beyond the cycle during which TAK-981 was discontinued.	Clarification.
7	Section 8.1.1 TAK-981 Study Drug Administration	Updated text to indicate that if infusion reactions are observed, the length of the infusion can be extended up to 2 hours (instead of up to 4 hours) for all patients without requiring a protocol amendment. Added that a dose delay of up to 7 days is allowed to accommodate for COVID-19 vaccine administration after discussion with the sponsor.	Alignment with the TAK-981 stability data when at room temperature. Guidance on COVID-19 vaccination timing and procedures during the study.
8	Section 8.7.6 COVID-19	Added a section describing criteria for restarting study treatment if a patient discontinued study treatment due to COVID-19 infection.	Guidance on treatment of patients with COVID-19.
9	Section 8.8.1 Excluded Concomitant Medications and Procedures for TAK-981	Added that vaccination during Cycle 1 is not permitted for patients in Phase 1b.	Vaccination during Cycle 1 in Phase 1b would confound safety evaluation and determination of dose-limiting toxicities.
10	Section 8.9 Permitted Concomitant Medications and Procedures	Added guidance on timing of COVID-19 vaccination during the study including live attenuated vaccine must be completed at least 4 weeks prior to treatment initiation, vaccination not permitted during Cycle 1 in Phase 1, vaccination to be avoided within ±3 days of TAK-981 administration, and allowing a 7-day dose delay to accommodate vaccination.	Guidance on COVID-19 vaccination timing and procedures during the study.
11	Section 9.4.15 Pharmacodynamics Measurements	Rearranged order of specimens and updated the specimens collected to align with Table A-5 and Table A-6.	Update to align with translational strategy for biomarker sample collection.
12	Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Updated contact information for reporting medication errors.	Administrative update.

Protocol Amendment 2			
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***
13	Appendix A	Updated Appendix A schedule of event (SOE) table numbers as Tables A-1 through A-6 instead of Tables 1 through 6. Updated Tables A-4, A-5, and A-6 to reflect streamlined PK and pharmacodynamic sample collection strategies.	Update to align with translational strategy for biomarker sample collection.
14	Appendix F Drugs that Interact With the CYP3A Family of Cytochromes P450	Under strong cytochrome P450 (CYP) 3A inhibitors deleted grapefruit. Added footnote b to separate sources for CYP3A inducers and inhibitors. Moved table footnote text to paragraph above table.	Update to align with current Food and Drug Administration guidance and with other TAK-981 protocols.
15	Appendix G Examples of Clinical Inhibitors of	Updated source.	Correction.
16	Appendix H iBOIN Design	Updated Appendix H table numbers as Tables H-1 through H-3 instead of Tables 1 through 3.	Update for consistency with other protocols.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound: TAK-981**
Title of Protocol: A Phase 1b/2 Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of TAK-981 in Combination With Monoclonal Antibodies in Adult Patients With Relapsed and/or Refractory Multiple Myeloma.	**EudraCT No.:** Not applicable
Study Number: TAK-981-1503	**Phase:** 1b/2

Study Design:

This study is an open-label, multicenter, Phase 1b/2 study investigating the combination of TAK-981 and monoclonal antibodies (mAbs) in adult patients with relapsed and/or refractory multiple myeloma (RRMM). The study will be conducted in 2 phases:

1. Phase 1b dose escalation of TAK-981 guided by Bayesian Optimal Interval Design with Informative Prior (iBOIN) in combination with fixed doses of mezagitamab or daratumumab and hyaluronidase-fihj, respectively in patients with RRMM.
2. Phase 2 study of TAK-981-based mAb combinations with multiple treatment arms in patients with RRMM.

Treatment cycle duration is 28 days. TAK-981 in combination with the mAbs will be administered for up to 24 cycles or until disease progression or unacceptable toxicity, whichever comes first. Patients with demonstrated clinical benefit may continue treatment beyond 24 cycles with the agreement of the sponsor/ designee.

Patient participation will include a screening phase, a treatment phase, and a follow-up phase. The screening phase will be up to approximately 28 days before Cycle 1 Day 1 (C1D1). The treatment phase will extend from C1D1 until patients experience disease progression or unacceptable toxicity, or until any other discontinuation criterion is met. The follow-up phase of the study begins once a patient discontinues study treatment and completes the end-of-treatment (EOT) visit; study follow-up continues until the study ends or the patient completes overall survival (OS) follow-up.

Primary Objectives:

The primary objectives are:

Phase 1b:

- To determine the safety and tolerability of TAK-981 in combination with mAbs in patients with RRMM.
- To determine the recommended Phase 2 dose (RP2D).

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with mAbs in patients with RRMM.

Secondary Objectives:

The secondary objectives are:

- To characterize the pharmacokinetic (PK) profile of TAK-981 in combination with anti-CD38 mAb.
- To assess immunogenicity of anti-CD38 monoclonal antibodies (mezagitamab and daratumumab) to help interpreting PK profile, efficacy and safety of TAK-981 in combination with monoclonal antibodies.

Phase 1b:

- To evaluate preliminary efficacy of the TAK-981-mAb combination according to standard International Myeloma Working Group (IMWG) criteria.
- To assess target engagement of TAK-981 (TAK-981- small ubiquitin-like modifier [SUMO] adduct formation) and SUMOylation pathway inhibition in blood.

Phase 2:

- To further characterize efficacy of TAK-981 in combination with anti-CD38 mAb in RRMM.
- To evaluate the safety and tolerability of TAK-981 in combination with anti-CD38 mAb.

Subject Population: Male or female subjects aged 18 years or older with RRMM.

Number of Patients:	**Number of Sites:**
Approximately 81 patients will be enrolled. Phase 1b Part 1: approximately 30 patients (approximately 15 patients in each dosing schedule). Phase 1b Part 2: approximately 15 patients. Phase 2: up to approximately 36 patients.	Estimated total: Approximately 15 sites in North America and/or globally
Dose Level(s):	**Route of Administration:**
TAK-981: 60, 90, and 120 mg. Mezagitamab: 600 mg. Daratumumab and hyaluronidase-fihj: 1800 mg	TAK-981: Intravenous infusion. Mezagitamab: Subcutaneous. Daratumumab and hyaluronidase-fihj: Subcutaneous.
Duration of Treatment: Patients will continue on the assigned therapy until disease progression, unacceptable toxicity, or to a maximum of 24 cycles, whichever occurs first	**Period of Evaluation:** The expected period of evaluation for this study is 36 to 48 months; approximately 12 months for enrollment for each phase and approximately 24 months for treatment and/or follow-up.

Inclusion Criteria:

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

1. Male or female patients aged 18 years or older.
2. Be willing and able to provide written informed consent for the study.
3. For patients with multiple myeloma (for Phase 1b and Phase 2):
    a. A prior diagnosis of multiple myeloma as defined by the IMWG criteria with documented disease progression.
    b. Has measurable disease defined as one of the following:
        - Serum M-protein ≥0.5 g/dL (≥5 g/L).
        - Urine M-protein ≥200 mg/24 hours.
        - In patients without measurable M-protein in serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal.
    c. Has undergone stem cell transplant or is considered transplant ineligible, and
        - Patients with a history of autologous stem cell transplant are eligible if the transplant was > 100 days prior to study consent.
    d. Has failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (eg, daratumumab, daratumumab and hyaluronidase-fihj, isatuximab) alone or in combination.,
    e. Is either refractory, or intolerant to at least 1 immunomodulatory drug ([IMiD]; ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 proteasome inhibitor (ie, bortezomib, ixazomib or carfilzomib), and refractory to at least 1 anti-CD38 antibody and who have demonstrated disease progression with the last therapy.
        - Refractory myeloma is defined as disease that is nonresponsive while on therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy.
        - A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a

combination of several drugs, or a planned sequential therapy of various regimens (eg, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by a stem cell transplantation, consolidation, and maintenance is considered 1 line).

4. Have a performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
5. Have suitable venous access for safe drug administration and the study-required blood sampling, including PK and pharmacodynamic sampling.
6. Have adequate organ function as specified below at screening:
    a. Platelet count ≥75, 000 mm^3 (≥75 × 10^9/L); value of ≥50,000 mm^3 (≥50 × 10^9/L) may be acceptable for patients with ≥50% bone marrow burden following discussion with the sponsor (Platelet transfusion will be allowed >3 days before assessment).
    b. Hemoglobin must be ≥8 g/dL. (red blood cell [RBC] transfusion allowed ≥14 days before assessment).
    c. Absolute neutrophil count (ANC) ≥1000 mm^3 (≥1.0 × 10^9/L); value of ≥750 mm^3 (≥0.75 × 10^9/L) may be acceptable for patients with ≥50% bone marrow burden following discussion with the sponsor.
    d. Estimated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/minute for patients with serum creatinine concentrations above the upper limit of normal range (ULN).
    e. Aspartate aminotransferase (AST, glutamic oxaloacetic transaminase [GOT]) and alanine aminotransferase (ALT, GPT) ≤3.0 × ULN; bilirubin ≤1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 × ULN, per discussion between the investigator and the medical monitor.
7. Have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.
   Note: Except neuropathy Grade ≤2, any grade alopecia, or bone marrow parameters [any of Grade 1 or 2 permitted if directly related to bone marrow involvement].
8. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 6 months after the last dose of drug in the combination. 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.)
9. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of drug in the combination, 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.)
10. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol.

Exclusion Criteria:

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

1. Received treatment with systemic anticancer treatments within 14 days before the first dose of study drug or any investigational products (IPs) within 5 half-lives of the first dose of study drug, whichever is appropriate to last therapy received. (eg, non- IP IMiD, proteasome inhibitor, anti-CD38 mAb could be considered to be eligible if there is at least 14 days after last dose before first dose of study drug).

   Note: Treatment with a single course of glucocorticoids (maximum dose of corticosteroids should not exceed the equivalent of 160 mg [for example, 40 mg/d for 4 days] of dexamethasone), hormonal therapy for prostate cancer or breast cancer (as adjuvant treatment), and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors are allowed.
2. Current participation in another interventional study, including other clinical trials with investigational agents (including investigational vaccines or investigational medical device for disease under study) within 4 weeks of the first dose of TAK-981 and throughout the duration of this trial.
3. Prior radiation therapy within 14 days of the first dose of TAK-981.

   Note: Prophylactic localized ("spot") radiation for areas of pain is allowed.
4. Major surgery within 4 weeks before C1D1. Patients should be fully recovered from any surgically related complications.

   Note: Kyphoplasty is not considered major surgery.
5. Plasmapheresis within 28 days of randomization.
6. Diagnosis of primary amyloidosis, Waldenström's disease, monoclonal gammopathy of undetermined significance or smoldering multiple myeloma (SMM) per IMWG criteria or standard diagnostic criteria, plasma cell leukemia (according to the World Health Organization criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), myelodysplastic syndrome, or myeloproliferative syndrome.
7. With disease where the only measurable parameter is plasmacytoma.
8. 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.
9. Evidence of central nervous system involvement and/or meningeal involvement of MM exhibited during screening.
10. Known severe allergic or anaphylactic reactions to human recombinant proteins or excipients used in the TAK-981 formulation or the mAbs (such as daratumumab or daratumumab and hyaluronidase-fihj as per the prescribing information and for mezagitamab as outlined in the mezagitamab investigator's brochure).
11. History of treatment discontinuation due to treatment-related toxicity to the combination partner (daratumumab or daratumumab and hyaluronidase-fihj).
12. Prior treatment with more than 1 anti-CD38 antibody.
13. Chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1 second (FEV1) <50% of predicted normal; or diagnosis of moderate or persistent asthma within the last 2 years, or currently uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed); pulmonary fibrosis; or history of symptomatic bronchospasm. Note that FEV1 testing is required for patients with known or suspected COPD or asthma and patients must have a FEV1 ≥50% of predicted normal during screening.
14. Any concurrent or uncontrolled medical, comorbid, or psychiatric condition or disease that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

15. History of HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
16. Systemic infection requiring systemic antibiotic therapy or other serious infection within 14 days before the first dose of TAK-981 or any agent in the combination.

    Note: Urinary tract infection is not considered a systemic infection.
17. 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.
18. Active or history of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
19. History of allogeneic tissue or solid organ transplant.
20. Receipt of any live vaccine (eg, varicella, pneumococcus) within 4 weeks of initiation of study treatment.
21. 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 F) or are strong P-glycoprotein (Pgp) inhibitors (Appendix G) at screening. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks or 5 times the half-life (whichever is shorter) before receiving a dose of TAK-981.
22. Require the use of drugs known to prolong the corrected QT interval (during Phase 1b only) (Appendix I).
23. 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, uncontrolled hypertension despite appropriate medical therapy, ongoing symptomatic cardiac arrhythmias >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.
24. Baseline prolongation of the QT interval with Fridericia's correction method (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes). If a machine reading is above this value, the electrocardiogram (ECG) should be reviewed by a qualified reader and confirmed on a subsequent ECG.
25. 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.
26. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
27. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a on Day 1 before first dose of TAK-981 study drug.

Main Criteria for Evaluation and Analyses:

The primary endpoints are:

Phase 1b:

- Frequency and severity of treatment-emergent adverse events (TEAEs) for all dose groups.
- Occurrence of dose-limiting toxicities (DLTs) in Cycle 1.

Phase 2:

- Overall response rate (ORR) (response of at least partial response [PR]) based on investigator's assessment according to standard IMWG disease response criteria.

The secondary endpoints are:

- TAK-981 concentration-time data.
- Anti-mezagitamab or anti-daratumumab antibody (ADA): negative, transient or persistent positive, high or low ADA titer.
- Sparse PK evaluations of mezagitamab or daratumumab.

Phase 1b:

- ORR, clinical benefit rate (CBR), duration of response (DOR), time to progression (TTP), time to next treatment (TTNT), progression-free survival (PFS), and overall survival (OS) based on IMWG criteria.
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood.

Phase 2:

- Frequency and severity of TEAEs.
- CBR, DOR, TTP, TTNT, PFS, and OS based on IMWG criteria.
- Percentage of participants with minimal residual disease (MRD) negative status as determined by next-generation sequencing (NGS).
- MRD negative rate at 1 year, defined as percentage of participants who have achieved MRD negative status at 1 year.
- Durable MRD negative rate, defined as the number of participants who have achieved MRD negative status (at 10^-5) at 2 bone marrow aspirates examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

Statistical Considerations:

The iBOIN design will be implemented for the dose escalation phase. It is estimated that up to approximately 30 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981 in combination with mezagitamab, with up to approximately 15 patients for each dosing schedule in Phase 1b Part 1.

After RP2D is determined in Phase 1b Part 1, dose escalation of TAK-981 in the combination with daratumumab will begin with a starting dose for TAK-981 1 dose level below RP2D. Dose escalation will follow the similar iBOIN design in Phase 1b Part 2. It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to confirm the dose in this combination.

After the RP2D has been determined in Phase 1b, patients with RRMM will be enrolled into a Phase 2 study evaluating TAK-981 in combination with either mezagitamab or daratumumab and hyaluronidase-fihj.

Sample Size Justification:

The iBOIN design will be implemented for the dose escalation phase. It is estimated that up to approximately 30 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981 combining with mezagitamab, with up to approximately 15 patients for each dosing schedule.

After RP2D is defined, dose for TAK-981 in the combinations of daratumumab and hyaluronidase-fihj will be evaluated using the similar iBOIN design. It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate dose escalation for this combinations.

[redacted]

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 (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ADA	antidrug antibody (exchangeable terminology for anti-mezagitamab or anti-daratumumab antibody in this protocol)
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BMA	bone marrow aspirate
BIW	twice weekly
C1D1	Cycle 1, Day 1
CBR	clinical benefit rate
CDC	complement dependent cytotoxicity
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DC	dendritic cell
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
[redacted]	[redacted]
FDA	[United States] Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
GOT	glutamic oxaloacetic transaminase
HBV	hepatitis B virus
HCV	hepatitis C virus
iBOIN	Bayesian Optimal Interval Design with Informative Prior

IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IFN	interferon
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IP	investigational product
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
ISS	International Staging System
IV	intravenous
IVRS/IWRS	integrated voice response system/interactive web response system
KM	Kaplan-Meier
mAb	monoclonal antibody
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MED ID	medication identification
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent-to-treat
MM	multiple myeloma
MOA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NGS	next-generation sequencing
NK	natural killer
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial response

[redacted]	[redacted]
QTc	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
RP2D	recommended Phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sCR	stringent complete response
SLE	systemic lupus erythematosus
SMC	Safety Monitoring Committee
SMM	smoldering multiple myeloma
SOE	schedule of events
SPEP	serum protein electrophoresis
SUMO	small ubiquitin-like modifier
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of the normal range
TTNT	time to next treatment
TTP	time to progression
UPEP	urine protein electrophoresis
UK	United Kingdom
US	United States
VGPR	very good partial response
V_{ss}	volume of distribution at steady state
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 Background

Multiple myeloma (MM) is a plasma cell-derived malignancy that accounts for approximately 1% of all cancers and 10% of hematologic malignant disorders [1]. It is characterized by proliferation of clonal malignant plasma cells in the bone marrow, lytic bone lesions, and immunodeficiency. Treatment of MM, especially relapsed is complicated and is characterized by relapses and remissions, with each remission typically lasting less than the prior one [2] MM Patients with successive relapses or who are refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors, and anti-CD38 monoclonal antibody (mAb) have poor survival, highlighting that novel therapies and treatment combinations are urgently needed [2].

CD38 is a surface protein that is highly expressed on plasma cells, and at relatively low levels on normal lymphoid, myeloid cells, as well as red blood cell (RBC) and platelets [3,4]. After plasma cells, CD38 is most strongly expressed on natural killer (NK) cells, with weaker expression on B cells and T cells [3]. CD38 is highly expressed in MM in addition to a subset of hematological tumors such as NK/T cell lymphoma, T Cell and B Cell acute lymphoblastic leukemia, acute myeloid leukemia, and plasma cell dyscrasias such as Waldenström's macroglobulinemia and systemic light chain amyloidosis [3].

Targeting the small ubiquitin-like modifier (SUMO) pathway may provide a novel therapeutic approach for hematologic malignancies. The SUMOylation pathway is often overexpressed in MM, as compared to normal B cells and plasma cells from healthy individuals. This overactivation of SUMOylation may represent a protective effect in MM cells and is associated with poor patient outcomes [5]. Inhibition of SUMOylation represents a novel therapeutic strategy in MM based on its link to type I interferon (IFN-I) regulation. Historically, IFNα treatment has played a role in the treatment of myeloma, although its use as a systemic therapy is limited by its toxicity and narrow therapeutic window [6]. A key role for SUMOylation in suppressing expression of IFN-Is was demonstrated by means of genetic knockout of the pathway in vivo in the myeloid compartment and ex vivo in dendritic cells (DCs), resulting in enhanced basal expression levels of IFN-Is and sensitization of IFN induction in response to pathogenic stimuli [7]. IFN-Is, such as IFNα and IFNβ are potent immunomodulatory cytokines induced early in the innate immune response which 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 [8,9]. They also directly act upon T cells to stimulate survival, clonal expansion and the development of T cell effector function [10,11]. IFN-Is also play a central role in propagating adaptive immune responses by promoting maturation of DCs and cross presentation of antigens to T cells [12,13].

4.1.1 TAK-981

4.1.1.1 Mechanism of Action

TAK-981 is a potent and selective mechanism-based inhibitor of the SUMO-activating enzyme which inhibits SUMOylation by forming a covalent adduct with SUMO when it is bound to the SUMO-activating enzyme. Central to the antitumor mechanism of action (MOA) of TAK-981 is its ability to induce expression of IFN-Is. Ex vivo assays demonstrated that TAK-981 promoted the activation of DCs, NK cells, T cells and macrophages in a IFN-I-dependent manner. The ability of TAK-981 to promote activation of macrophages and NK cells provides a mechanistic rationale for its use in combination with anti-tumor antibodies reliant on antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cell-mediated phagocytosis (ADCP), such as rituximab, daratumumab, and mezagitamab. In ex vivo assays, TAK-981 upregulated inflammatory markers on macrophages (CD80, CD86) and increased the phagocytic activity of monocyte-derived macrophages in both the absence and presence of the mAbs rituximab and daratumumab in a IFN-I-dependent manner. TAK-981 increased the activation marker CD69 and the degranulation marker CD107 on NK cells and enhanced the cytotoxicity of NK cells in both the absence and presence of rituximab. In vivo, TAK-981 showed synergy with the anti-CD20 antibody rituximab in OCI-Ly10 xenografts in severe combined immunodeficiency mice (lacking B cells and T cells but retaining an intact innate immune system). In vivo experiments in Daudi lymphoma xenografts, which express both CD20 and CD38, demonstrated synergy between TAK-981 and rituximab and between TAK-981 and the anti-CD38 antibodies daratumumab and mezagitamab. These studies showed that the combination of TAK-981 with mezagitamab or daratumumab was well tolerated with no synergistic toxicity. There was no treatment-related mortality or maximum mean body weight loss greater than 10% in the combination groups.

Figure 4.a Synergistic Combination of TAK-981 With Daratumumab or Mezagitamab (TAK-079) in the Daudi Tumor Model.

BIW: twice weekly.

TAK-981 combines synergistically with daratumumab or mezagitamab (TAK-079) in the Daudi tumor model. Eight week-old female CB-17 severe combined immunodeficiency mice were inoculated subcutaneously in the flank with 2×10^6 Daudi cells. When the mean tumor volume reached approximately 100 to 200 mm^3, animals were randomized into treatment groups (n =8/group) and dosed intravenously with TAK-981, intraperitoneally with daratumumab or mezagitamab, or with the combination of TAK-981 with either daratumumab or mezagitamab at 7.5 mg/kg twice per week for 3 weeks (D0/D5/D8/D12/D15/D19).

4.1.1.2 Nonclinical Pharmacokinetics

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

In plasma, after single intravenous (IV) administration, TAK-981 showed moderate to high plasma clearance and volume of distribution at steady state (V_{ss}) after IV administration in mice, rats, dogs, and monkeys with half-lives varying from 2 to 6 hours among species. For latest information, refer to the TAK-981 investigator's brochure (IB).

4.1.1.3 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 to baseline body temperature of 37.8ºC to 38.9ºC). Increased body temperature (0.5°C to 2.0°C) was also observed in dogs at ≥3 mg/kg in a single-dose cardiovascular assessment study and after repeat once-daily or once weekly (QW) dosing. Increased body temperature in the cardiovascular assessment study was not associated with effects on blood pressure or electrocardiogram (ECG) morphology but was associated with increased heart rate. Because intermittent dosing on a QW or twice weekly (BIW) schedule was demonstrated to be efficacious in mouse models, both QW and BIW schedules were examined in Good Laboratory Practices toxicology studies. Once per week 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, in Phase 1b Part 1 both the BIW and weekly schedules will be evaluated. One of the schedules will be selected for further evaluation in Phase 1b Part 2 and Phase 2.

The primary toxicity with BIW dosing was dose-dependent mild to marked decreases in peripheral blood lymphocyte counts that affected T cells, T cell subsets (helper, cytotoxic, activated, memory, regulatory), B cells, and NK cells approximately equally. Decreases in lymphocyte count were associated with decreases in lymphoid cellularity in the primary and secondary lymphoid organs including the thymus, spleen, lymph nodes, and gut-associated lymphoid tissue. Decreases in other circulating cell types including neutrophils, monocytes, basophils, and/or eosinophils were also observed, but were of decreased severity compared to decreases in lymphocyte counts. Additional effects observed with BIW dosing were limited to myeloid hyperplasia in the bone marrow in rats at 10 mg/kg and in dogs at 4 mg/kg; modest increases in serum monocyte chemotactic protein-1 (MCP-1), IFN gamma-induced protein 10 (IP-10) (rats only), and RANTES (regulated upon activation normal T cell expressed and secreted) (rats only) at ≥0.5 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, endocrine system, glandular organs, and reproductive tract (rat only). All target organ toxicities at tolerated doses were considered to be monitorable, except for inflammation and vascular necrosis in the renal pelvis in dogs. All target organ toxicities were completely or partially reversible.

An in vitro cytokine release assay was performed to evaluate the risk of TAK-981 to produce clinically significant CRS and was considered negative.

For the latest information, refer to the TAK-981 IB.

4.2 Clinical Experience

4.2.1 TAK-981

TAK-981 is being evaluated in an ongoing first-in-human (FIH) Phase 1 study evaluating safety in patients with advanced or refractory solid tumors or lymphomas (Study TAK-981-1002), and 2 ongoing Phase 1b/2 clinical efficacy and safety studies; 1 in combination with rituximab in patients with relapsed/refractory indolent or aggressive CD20+ non Hodgkin lymphomas (Study TAK-981-1501) and 1 in combination with pembrolizumab in patients with select advanced or metastatic solid tumors (Study TAK-981-1502).

As of the 28 June 2021 data cutoff for the IB, 135 patients have been treated with TAK-981 across 4 clinical trials; 81 patients have received single agent TAK-981 and 55 patients have received TAK-981 as part of a combination regimen. Overall, TAK-981 has been well tolerated

and the type of treatment-emergent adverse events (TEAEs) are consistent with induction of interferon signaling or were consistent with the patients' underlying cancer disease (see Section 4.5.1 and Section 8.11 for more details). The most common TEAEs (>20%) in the total population in Studies TAK-981-1002, TAK-981-1501, and TAK-981-1502 are fatigue, pyrexia, nausea, diarrhea, chills, and headache (Table 4.a). Overall, preliminary efficacy is being observed, and efficacy evaluations are ongoing. (Refer to current TAk-981 IB for details).

Table 4.a Most Frequent (≥10% of All Patients) TEAEs in Studies TAK-981-1002, TAK-981-1501, and TAK-981-1502

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

Source: TAK-981 Investigator's Brochure Edition 4, Table 5.g (Data cut-off date: 28 June 2021).
TEAE: treatment-emergent adverse event.

In study TAK-981-1002, the maximum tolerated dose (MTD) was determined to be 120 mg; the recommended Phase 2 dose (RP2D) for single agent TAK-981 is 90 mg given BIW (Days 1, 4, 8, 11) in a 21-day cycle. Out of the 81 patients, 4 dose-limiting toxicities (DLTs) were reported in the single-agent study: transient Grade 3 serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations at 60 mg BIW, Grade 3 recurrent pneumonitis after a previous pneumonitis with an anti-progressive disease-1 (PD-1) inhibitor at 90 mg BIW, and 2 at 120 mg BIW, transient Grade 3 stomatitis and transient Grade 3 cognitive disturbance with Grade 2 lethargy. The most common (≥20%) TEAEs in Study TAK-981-1002 across 10 dose levels (3 mg-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.

Refer to the TAK-981 IB for additional details.

4.2.2 Daratumumab

Daratumumab and hyaluronidase-fihj (Darzalex FASPRO) is an immunoglobulin GI kappa (IgG1κ) human mAb that binds to CD38 antigens and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis, complement dependent cytotoxicity (CDC), ADCC, and ADCP. Daratumumab has an acceptable clinical safety profile and is approved as a monotherapy and in combination with standard anti-myeloma therapies for patients with MM [14,15].

4.2.3 Mezagitamab

Mezagitamab (TAK-079), is an investigational IgG1 human mAb directed against CD38. Compared to daratumumab, mezagitamab shows lower affinity binding to CD38 expressed on RBCs and platelets, and greater affinity binding to CD38 on blood B and T lymphocytes [16]. It depletes myeloma cells through apoptosis, ADCC, CDC, and ADCP [17]. Mezagitamab monotherapy has been shown to be safe, generally well tolerated, and active in patients with relapsed and/or refractory multiple myeloma (RRMM) through tested doses (45, 135, 300, 600, and 1200 mg). Clinical activity occurred early and was durable. No MTD has been identified. No infusion-related reactions (IRRs) and no significant hematologic toxicity has been reported. The RP2D is 600 mg. Progression-free survival (PFS), with a median FU of 7.5 months at the data-cut off, is not estimable at the RP2 dose [18]. Clinical studies are ongoing in MM (relapsed/ refractory and newly diagnosed), systemic lupus erythematosus (SLE), myasthenia gravis, and primary immune thrombocytopenia purpura. Additionally a study in healthy volunteers has been completed. Refer to the Mezagitamab IB for additional details.

4.3 Rationale for the Proposed Study

The treatment of patients with MM is challenging even with the therapies approved in recent years. Patients with disease refractory to IMiDs, proteasome inhibitors, and anti-CD38 mAbs have a poor prognosis owing to a changing biology and development of drug resistant phenotypes within the tumor. The role of the physical interaction between MM cells and the bone marrow microenvironment in myeloma pathogenesis is well documented [19]. This reality has driven the search for new agents and combinations that could be effective in patients with RRMM. Therapies that engage the immune system to treat MM may offer significant clinical benefit to such patients [20].

TAK-981 is a first-in-class inhibitor of SUMOylation that stimulates innate and adaptive immune responses and may potentially offer transformative clinical benefits to patients with hematologic malignancies. Ongoing Phase 1 studies have demonstrated acceptable PK characteristics with an acceptable and manageable safety profile. Based on its MOA, evaluation in patients with RRMM, patients with a high unmet medical need, is warranted.

There is strong nonclinical evidence demonstrating that TAK-981 can synergize with mAbs against CD38 and other targets relevant in hematological malignancies such as CD20. TAK-981 induces IFN-I signaling and as a consequence activates NK cells and polarizes macrophages towards an M1 phenotype, which enhances ADCC and ADCP. These antibody-dependent effector mechanisms are a major contributor to the antitumor effects of IgG1 mAbs, providing a mechanistic rationale for the use of TAK-981 in combination. Preclinical studies have demonstrated combination benefit in vitro and in vivo with the therapeutic mAbs rituximab, daratumumab, and mezagitamab. An additional rationale for the use of TAK-981 in combination with anti-CD38 mAbs is that CD38 expression levels can increase in response to IFN-I signaling [21], which could restore or promote sensitivity to anti-CD38 mAbs in cases where its expression is low. Clinical trials are underway with TAK-981 as a single agent in patients with advanced solid tumors and relapsed/refractory hematological malignancies (NCT03648372), with TAK-981 in combination with rituximab in patients with relapsed/refractory CD20+ lymphoma (NCT04074330), and with TAK-981 in combination with the checkpoint inhibitor pembrolizumab in patients with advanced solid tumors [NCT04381650]. This Phase 1b/2 trial proposes to study the combination of TAK-981 with the anti-CD38 mAbs daratumumab and mezagitamab in patients with CD38 positive hematologic malignancies, ie, RRMMs.

4.4 Rationale for the Starting Dose and Schedule

TAK-981 has been extensively characterized in preclinical studies (Refer to the TAK-981 IB for the latest information) and is in the early stages of clinical investigation. The initial dose of TAK-981 was selected from the dose escalation portion of the FIH study TAK-981-1002, a Phase 1/2 study of TAK-981 in patients with advanced or metastatic solid tumors or relapsed/refractory hematologic malignancies. As of the IB data cutoff at the time of the initial TAK-981-1503 protocol development (28 June 2020), Study TAK-981-1002 enrolled 31 patients and had completed dose escalation across 7 dose cohorts (3, 6, 10, 15, 25, 40, and 60 mg) with enrollment ongoing in cohort 8 (90 mg) on Days 1, 4, 8, and 11 (every 3 weeks). Across the doses tested at that time, the PK of TAK-981 was linear and indicated minimal or no accumulation [current TAK-981 IB], the MTD had not been reached, and the most common TEAE reported was fatigue.

Two DLTs had been observed; 1 each at the 60 and 90 mg dose levels. The DLT observed at 60 mg consisted of a transient Grade 2 serum ALT and AST evaluation with normal bilirubin after the third dose of TAK-981. The patient did not have a history of liver metastasis or fatty liver, and was not taking confounding concomitant medications. The ALT and AST elevations resolved within 72 hours, TAK-981 was resumed at 40 mg, and no further alterations of the liver function tests were observed in the subsequent TAK-981 doses. The DLT observed at 90 mg consisted of Grade 3 pneumonitis. The patient was previously treated with 3 check point inhibitor-containing regimens and had a previous episode of immune-related pneumonitis that led to dual anti-CTLA-4 and anti-PD-1 blockade discontinuation 6 months before the initiation of TAK-981 treatment. The patient reported fever and increasing fatigue; Grade 4 lymphopenia with C-reactive protein of 149.6 mg/L were observed. Blood cultures for bacterial infection in addition to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain

reaction test were negative. Computed tomography (CT) scan of the chest confirmed ground glass opacities compatible with recurrent pneumonitis. The patient was discharged after 12 days of treatment with IV steroids and subsequent oral prednisone tapering with mild residual opacities in the radiology evaluation.

Based on the available safety, pharmacodynamic, and PK data at the time of this protocol development, the starting dose of TAK-981 will be 60 mg. This starting dose level of TAK-981 is 1 dose level below the monotherapy dose that cleared the DLT period (90 mg) and 2 dose levels below the current dose escalation cohort (120 mg) in the ongoing FIH single agent study (Study TAK-981-1002). Early pharmacodynamic studies of patient samples collected in TAK-981-1002 provide evidence of dose-dependent target engagement (TAK-981-SUMO adduct) in blood and skin, evidence of SUMO pathway inhibition in blood and skin, and induction of a IFN-I response at 60 mg assessed by several complementary methods (gene expression in blood, increase in plasma cytokines and chemokines, and increased CD69 expression on NK cells).

The individual mAbs included in this study are given in a 28-day cycle. Therefore, the TAK-981 schedule will also be adapted to a 28-day cycle. TAK-981 will be given on Days 1, 4, 8, 11, and 15, in Cycles 1 and 2, followed by 1 dose every 2 weeks in Cycle 3 to 6, and then once every 4 weeks dosing thereafter (See Section 8.0). The adapted TAK-981 BIW dosing schedule allows for >10 days of hematopoietic recovery in the event that lymphocytopenia emerges as a DLT in the 28-day cycle. To date, reductions in lymphocyte counts have been mild and transient with full recovery over 72 hours with TAK-981 dosing on Day 1, Day 4, Day 8, and Day 11 of a 15-day cycle. This approach will allow this study to start safely at a dosing schedule of 5 doses in a 28-day cycle; a total dose that is lower than that already safely evaluated in study TAK-981-1002 where 6 doses are delivered over the course of the first 28 days. A second schedule will evaluate TAK-981 given weekly in a 28-day cycle during cycle 1 and 2. The weekly schedule, TAK-981 administration on Day 1 and Day 8 of a 21-day cycle, is being explored in Study TAK-981-1002 and TAK-981-1501 to assess the impact of dose schedule intensity on safety and pharmacodynamic endpoints. The dose of 90 mg weekly on Day 1 and 8 has cleared the DLT period and the 120 mg cohort is now open for enrollment.

During the CD38 mAb taper from weekly dosing for C1 and C2 to twice monthly dosing for C3 to C6 and once every 4 weeks dosing thereafter, the schedule of TAK-981 administration was aligned with CD38 mAb administration and was primarily driven by practical considerations with regards to the treatment burden in MM patients. Overall, the emerging safety, efficacy, pharmacodynamic and PK data will guide the selection of the RP2D and schedule.

4.5 Potential Risks and Benefits

4.5.1 Potential Effects of TAK-981

The potential AEs/risks of TAK-981 are based on findings from the nonclinical studies with TAK-981 and the emerging safety data from ongoing clinical studies: hematologic effects (lymphocytopenia with/without associated opportunistic infection; anemia, thrombocytopenia, neutropenia); injection site reactions; IRRs and potential for CRS; changes in renal function

(Refer to Section 8.11). Safety data (as of 28 June 2021) obtained from the dose escalation cohorts across all ongoing studies demonstrated that the most common TEAEs (>20%) are fatigue, pyrexia, nausea, diarrhea, chills, and headache; TEAEs consistent with induction of IFN signaling. The only serious adverse reaction considered expected for safety reporting purposes across the ongoing TAK-981 studies is pyrexia. The single agent MTD (in Study TAK-981-1002) has been identified as 120 mg with evaluation continuing in the ongoing studies of TAK-981 in combination with rituximab or pembrolizumab (studies TAK-981-1501 and TAK-981-1502, respectively). For additional details, refer to the TAK-981 IB.

4.5.2 Potential Effects of Daratumumab and Hyaluronidase-fihj

The most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory infection, neutropenia, IRRs, thrombocytopenia, anemia, leukopenia, and lymphocytopenia [15]. Refer to Section 8.11 and daratumumab and hyaluronidase-fihj Prescribing Information for more details.

4.5.3 Potential Effects of Mezagitamab

The potential effects of mezagitamab are based on findings from the nonclinical studies with mezagitamab and the emerging safety data from ongoing clinical studies. The most common (in ≥ 15% of patients receiving monotherapy) TEAEs by preferred terms regardless of causality as of 20 March 2021 data cut off are fatigue and upper respiratory tract infection (27% each), insomnia and back pain (20% each), diarrhea, nausea, and anemia (16% each). Very limited injection site reactions have been reported (0.21%; including mild pruritis, moderate swelling at site). Thrombocytopenia/decrease in platelet count has been generally low grade and not clinically important. No DLTs have been reported with monotherapy. The MTD was not identified. No systemic infusion reactions, including documented CRS or anaphylaxis, have been reported. Refer to Section 8.11 and Mezagitamab IB for additional details.

4.5.4 Overall Benefit-Risk Assessment

The emerging preliminary safety profile, as summarized in Section 8.11, with further details in the current IBs, indicate that TAK-981 and mezagitamab are generally well tolerated with manageable and reversible AEs. Daratumumab and hyaluronidase-fihj has an acceptable clinical safety profile and is approved for patients with MM. The potential toxicities of all agents can be managed by clinical monitoring and standard medical interventions. It is possible that TAK-981 will have toxicities that were not predicted from its evaluation in nonclinical studies, or previously observed in ongoing clinical studies. To mitigate the inherent risks in clinical studies of TAK-981, patients will be carefully monitored closely for signs and symptoms of IRRs, CRS, hematologic toxicity, lymphopenia and opportunistic infections, and infusion site reactions with appropriate management of these events (see Section 8.11). Depending on the severity of the reaction, the TAK-981 drug dosage can be modified (ie, dose hold, delay or discontinued within a cycle) as outlined in Section 8.7.3.

In the ongoing clinical studies, TAK-981 has shown early signs of antitumor activity as a single agent and in combination with rituximab.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of TAK-981.

4.5.5 Coronavirus Disease 2019 Pandemic

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

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

Phase 1b:

- To determine the safety and tolerability of TAK-981 in combination with mAbs in patients with RRMM.
- To determine the RP2D.

Phase 2:

- To evaluate the efficacy of TAK-981 in combination with mAbs in patients with RRMM.

5.1.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK profile of TAK-981 in combination with anti-CD38 mAb.
- To assess immunogenicity of anti-CD38 monoclonal antibodies (mezagitamab and daratumumab) to help interpreting PK profile, efficacy and safety of TAK-981 in combination with monoclonal antibodies.

Phase 1b:

- To evaluate preliminary efficacy of the TAK-981-mAb combination according to standard International Myeloma Working Group (IMWG) criteria.
- To assess target engagement of TAK-981 (TAK-981-SUMO adduct formation) and SUMOylation pathway inhibition in blood.

Phase 2:

- To further characterize efficacy of TAK-981 in combination with anti-CD38 mAb in RRMM

- To evaluate the safety and tolerability of TAK-981 in combination with anti-CD38 mAb.

5.1.3 Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

Phase 1b:

- Frequency and severity of TEAEs for all dose groups.
- Occurrence of DLT in Cycle 1.

Phase 2:

- ORR (response of at least partial response [PR]) based on investigator's assessment according to standard IMWG disease response criteria.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- TAK-981 concentration-time data.
- Anti-mezagitamab or anti-daratumumab antibody (ADA): negative, transient or persistent positive, high or low ADA titer.
- Sparse PK evaluations of mezagitamab or daratumumab

Phase 1b:

- ORR, clinical benefit rate (CBR), DOR, time to progression (TTP), time to next treatment (TTNT), PFS, and overall survival (OS) based on IMWG criteria.
- TAK-981-SUMO adduct formation and SUMO pathway inhibition in blood.

Phase 2:

- Frequency and severity of TEAEs.
- CBR, DOR, TTP, TTNT, PFS, and OS based on IMWG criteria.
- Percentage of Participants with MRD negative status as determined by next-generation sequencing (NGS).
- MRD negative rate at 1 year, defined as percentage of participants who have achieved MRD negative status at 1 year.
- Durable MRD negative rate, defined as the number of participants who have achieved MRD negative status (at 10^{-5}) at 2 bone marrow aspirates (BMAs) examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

5.2.3 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN

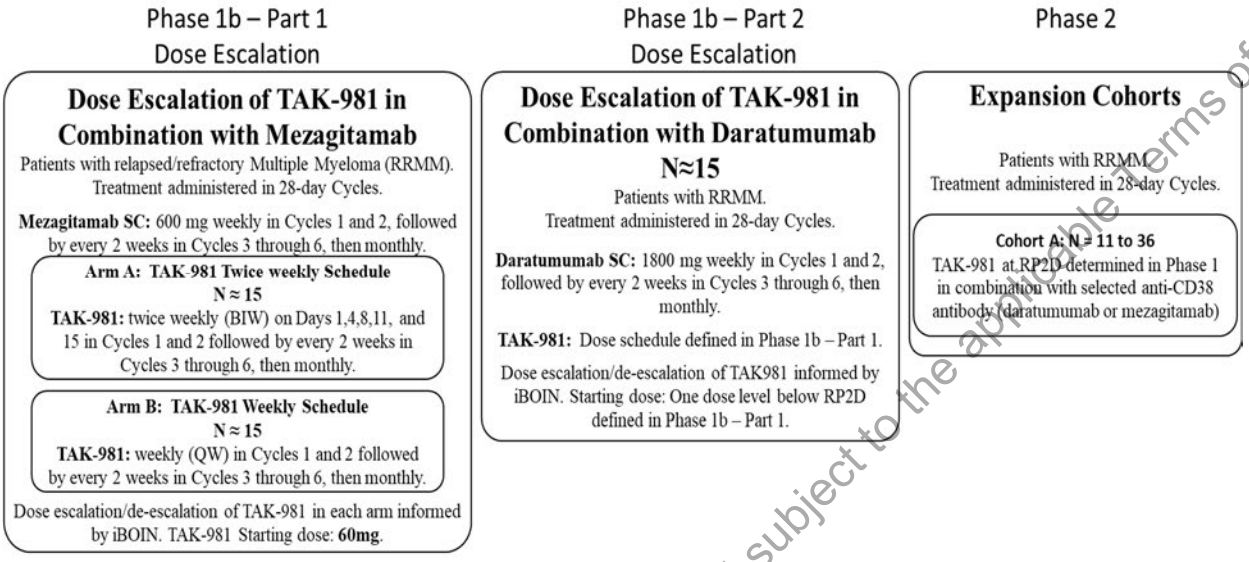
6.1 Overview of Study Design

This study is an open-label, multicenter, Phase 1b/2 study investigating the combination of TAK-981 and mAbs in adult patients with RRMM. The study will be conducted in 2 phases (Figure 6.a):

1. Phase 1b dose escalation of TAK-981 guided by Bayesian Optimal Interval Design with Informative Prior (iBOIN) in combination with fixed doses of mezagitamab or daratumumab and hyaluronidase-fihj, respectively in patients with RRMM.
2. Phase 2 study of TAK-981-based mAb combination in patients with RRMM.

Treatment cycle duration is 28 days. TAK-981 in combination with the mAbs will be administered for up to 24 cycles or until disease progression or unacceptable toxicity, whichever comes first. Patients with demonstrated clinical benefit may continue treatment beyond 24 cycles with the agreement of the sponsor/ designee. (TAK-981 study drug administration details in Section 8.1.1; Section 6.5.5 for poststudy access modalities).

Figure 6.a Study Schema



Patient participation will include a screening phase, a treatment phase, and a follow-up phase (see Section 9.0). The screening phase will be up to approximately 28 days before Cycle 1, Day 1 (C1D1). The treatment phase will extend from C1D1 until patients experience disease progression or unacceptable toxicity, or until any other discontinuation criterion is met (Refer to Section 9.7). The follow-up phase of the study begins once a patient discontinues study treatment and completes the end-of-treatment (EOT) visit; study follow-up continues until the study ends or the patient completes OS follow-up (Refer to Section 9.10).

6.2 Phase 1b Study Design

The Phase 1b part of the study will enroll patients with RRMM with the purpose of defining the RP2D and schedule of TAK-981 in combination with mezagitamab and daratumumab and hyaluronidase-fihj, respectively. The first part of the Phase 1b will determine the dose and schedule of TAK-981 in combination with a fixed dose and schedule of mezagitamab for expansion in Phase 2. The second part of the Phase 1b will determine the dose of TAK-981 for the combination with daratumumab and hyaluronidase-fihj.

6.2.1 Phase 1b Part 1

Dose escalation of TAK-981 will be guided by a iBOIN (see Section 8.5 and Appendix H for details). Up to approximately 15 patients will be enrolled to each of the TAK-981 schedules until either MTD or a pharmacologically active dose (PAD) is identified:

- Arm A: TAK-981 given IV BIW on Days 1, 4, 8, 11, and 15 in Cycles 1 and 2 followed by every 2 weeks in Cycles 3 through 6, then once every 4 weeks. TAK-981 will be given in combination with mezagitamab (Further details in Section 8.0).

- Arm B: TAK-981 given IV weekly (QW) on Days 1, 8, 15, and 22 in Cycles 1 and 2 followed by every 2 weeks in Cycles 3 through 6, then once every 4 weeks. TAK-981 will be given in combination with mezagitamab (Further details in Section 8.0).

The starting dose for TAK-981 will be 60 mg; the rationale for the initial TAK-981 dose is provided in Section 4.4. The dose of mezagitamab is the established RP2D at 600 mg.

Once enrolled into the study, patients will be assigned to a treatment arm in a nonrandomized, sequential manner based upon the recruitment status of the TAK-981 arm schedule, as communicated by the sponsor/ designee. A minimum of 3 patients will be enrolled in the first dose cohort. In the first dose cohort, patient enrollment will be staggered between the first and second patients by 7 days. The second and third patients can be dosed concurrently if the first patient in the cohort has gone through the Day 8 visit without clinically significant acute toxicities. Subsequent dose cohorts will not require staggering between patients.

Dose escalation will begin with the BIW schedule. TAK-981 dose escalation will be evaluated separately for each of the TAK-981 schedules.

Dose escalation decisions will be made by a Safety Monitoring Committee (SMC), composed of the principal investigators and sponsor. The SMC will regularly review safety data to ensure patients' safety throughout the Phase 1b portion of the study. Dose escalation will follow an iBOIN design. Dose escalation decisions will take into consideration primarily the DLTs observed in Cycle 1 in the patients enrolled in each dose level/schedule according to the rules in Section 8.5 (DLT rules). Available safety information beyond Cycle 1, PK and pharmacodynamic information from previously dose patients will also be considered.

Evaluation of intermediate doses or doses up to the maximum dose of 160 mg (the maximum dose level permitted in TAK-981-1002 FIH study), alternative dosing schedules (dosing interval), and expansion of an existing dose level are all permissible following agreement by the SMC, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, efficacy, exposure, or pharmacodynamics of TAK-981. The dose escalation/de-escalation rules based on iBOIN design will be considered as a guidance for the next dose level, however, the final decision on the dose will be made by the SMC.

6.2.1.1 Selection of RP2D for TAK-981 in Combination With Mezagitamab

The selection of an RP2D which includes the dose level and schedule of TAK-981 in combination with mezagitamab will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 1 portion of the trial which will include, but is not limited to safety data, preliminary PK data, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity. The RP2D may not be higher than the MTD as determined by iBOIN. Upon review of available Phase 1b data and agreement on the RP2D by the SMC, the Phase 1b Part 2 portion of the study of the combination of TAK-981 with daratumumab and hyaluronidase-fihj may begin.

6.2.2 Phase 1b Part 2

In the second part of Phase 1b, the RP2D of TAK-981 in combination with daratumumab and hyaluronidase-fihj will be determined.

Dose escalation of TAK-981 will be guided by iBOIN as described in Section 8.5. The starting dose for TAK-981 will be 1 dose-level below the RP2D defined for the combination with mezagitamab in Phase 1b Part 1 (RP2D-1). A minimum of 3 patients will be enrolled in the first cohort of this combination, and up to approximately 15 patients will be enrolled for the dose escalation.

6.2.2.1 Selection of RP2D for TAK-981 in Combination With Daratumumab and Hyaluronidase-fihj

The selection of an RP2D of TAK-981 in combination with daratumumab and hyaluronidase-fihj will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 2 portion of the trial which will include, but is not limited to safety data, preliminary PK data, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity. The RP2D may not be higher than the MTD as determined by iBOIN.

6.2.3 Selection of CD38 Antibody for Phase 2

The selection of the anti-CD38 antibody (mezagitamab or daratumumab and hyaluronidase-fihj) for combination with TAK-981 in Phase 2 will be made by the sponsor following evaluation of the available data from the Phase 1b – Part 1 portion of the trial which will include, but is not limited to safety data, selected RP2D, frequency of dose reduction/discontinuation observed for anti-CD38 antibody, preliminary pharmacodynamic data, preliminary translational data, PK/pharmacodynamic modeling and preliminary antitumor activity.

6.3 Phase 2 Study Design

The Phase 2 portion of the study will explore the efficacy and safety of TAK-981 in combination with an anti-CD38 antibody (mezagitamab or daratumumab and hyaluronidase-fihj) in patients with RRMM. Patients will be treated with the RP2D defined in Phase 1b for the respective antibody. Cycle duration is 28 days and treatment will be administered for up to 24 cycles or until disease progression or unacceptable toxicity, whichever occurs first. TAK-981, mezagitamab, and daratumumab and hyaluronidase-fihj administration details are in Section 8.0.

An adaptive 2-stage design for a single proportion will be used in Phase 2. For Stage I, each cohort will be analyzed when a prespecified number of patients (as defined in Section 13.0) have been enrolled and had the opportunity to complete 4 cycles of treatment. Enrollment may be paused until the Stage I analysis is completed. If the prespecified minimal response rate is not achieved in the first stage, enrollment will be closed. If the required response rate during Stage I or a good CBR is observed as mentioned above, then additional patients will be enrolled in the second stage of the corresponding cohort until a predetermined number of additional patients has been reached (as defined in Section 13.0). The final analysis of the primary endpoints will take

place when all ongoing patients have had the opportunity complete the 12-month disease assessment.

6.3.1 Early Stopping Rules

In the Phase 2 portion of the study, Grade 4 or higher drug-related AEs will be monitored starting from the first 11 response-evaluable patients and then every 4 response-evaluable patients up to the approximate maximum number of patients 36.

Accrual to the study will be suspended if:

- Grade 4 drug-related AEs meet the stopping bounds of the number of ≥4/11, ≥4/15, ≥5/19, ≥6/23, ≥7/27, ≥7/31, ≥8/35, ≥8/36; or
- At any time if 1 or more patients present with fatal drug-related AEs.

After review and consideration by the SMC, a decision will be made as to whether accrual can be resumed.

The stopping bounds for Grade 4 drug-related AEs are based on a Bayesian strategy to monitor outcomes in clinical trials. If the stopping rule is met, there is 80% probability that the true toxicity rate is greater than 16% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate [22].

6.4 Number of Patients

Overall this study will enroll up to approximately 81 patients in North America and/or globally. Approximately 15 patients will be enrolled in each dosing schedule in Phase 1b Part 1 and in Phase 1b Part 2. Up to approximately 36 patients will be enrolled in Phase 2. Approximately 15 sites will participate in this study.

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

6.5 Duration of Study

6.5.1 Duration of an Individual Patient's Study Participation

Patients may receive the TAK-981 mAb combination for up to 24 cycles or until they experience PD or unacceptable toxicity, or until any other discontinuation criterion is met, whichever occurs first (see Section 9.7).

Patients will be followed for up to 30 days after their last dose of TAK-981, or until the start of a subsequent alternative anticancer therapy to permit the detection of any delayed treatment-related AEs (this is the EOT visit). For patients who discontinue study drug before PD, disease evaluations should continue to be performed as specified in the schedule of events (SOE). Patients who discontinue for PD will be followed for survival after documented PD for up to 12 months after the last patient discontinues or completes treatment, or until loss of

follow-up, consent withdrawal, death, study termination, or until ≥50% of patients in the cohort have died, whichever occurs first. (see details in Section 9.6 and the SOE Appendix A).

6.5.2 End of Study/Study Completion Definition and Planned Reporting

The analyses for the CSR will be conducted after all patients enrolled in the study have had the opportunity to complete 1 year of therapy. See Section 6.5.5 for patients still benefiting from treatment.

Patients who discontinue a mAb for reasons described in Section 9.5 may continue TAK-981 treatment; however, once TAK-981 has been discontinued, patients cannot remain on the mAb as a single agent beyond the cycle during which TAK-981 was discontinued (ie, the patient can complete the planned mAb after TAK-981 was discontinued in the same cycle, but the mAb can not continue in subsequent cycles). In that case, patients will undergo the EOT visit.

6.5.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary (Phase 1b):		
Frequency and severity of TEAEs per dose level	Standard safety assessments [a]	Up to 24 months
Occurrence of DLTs in Cycle 1 per dose level	Standard safety assessments	Up to 24 months
Primary (Phase 2):		
ORR defined by the investigator according to IMWG disease response criteria	ORR	Up to 24 months
Secondary:		
Data permitting for dose escalation cohorts, PK parameters after the dose administration of TAK-981 on C1D1 : C_{max}, t_{max}, AUC_t, AUC_∞, $t_{1/2z}$, CL, V_{ss}	Standard PK parameters to allow determination of PK profile	Up to 24 months
ADA negative, ADA transient or persistent positive, high or low ADA titer	ADA negative, ADA transient or persistent positive, high or low ADA titer	Up to 24 months
ORR	ORR	Up to 24 months
CBR	CBR	Up to 24 months
DOR	DOR	Up to 24 months
TTP	TTP	Up to 24 months
PFS	PFS	Up to 24 months
OS	OS	Up to 24 months
MRD	MRD	Up to 24 months
TAK-981-SUMO adduct formation, and SUMO pathway inhibition	TAK-981-SUMO adduct formation, and SUMO pathway inhibition in blood	Up to 24 months
Frequency and severity of TEAEs	Standard safety assessments [a]	Up to 24 months

AUC_t: area under the plasma/blood/serum concentration-time curve from time 0 to time $_t$; AUC_∞: area under the plasma concentration-time curve from time 0 to infinity; C1D1: Cycle 1, Day 1; CBR: clinical benefit rate; CL: total clearance after intravenous administration; C_{max}: maximum observed plasma concentration; CT: computed tomography; DLT: dose-limiting toxicity; DOR: duration of response; FDA: Food and Drug Administration; IMWG: International Myeloma Working Group; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; SAE: serious adverse events; SUMO: small ubiquitin-like modifier; TEAE: treatment-emergent adverse event; $t_{1/2z}$: terminal disposition phase half-life; TTP: time to progression; t_{max}: time of first occurrence of C_{max}; V_{ss}: volume of distribution at steady state after intravenous administration.

[a] Phase 1b and 2 safety for CT.gov will be disclosed in only 1 section of ClinicalTrials.gov results database. Reporting will follow the requirements of Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801)

6.5.4 Total Study Duration

It is anticipated that this study will last for approximately 36 to 48 months.

6.5.5 Posttrial Access

Patients who have met the primary (and secondary) endpoints of the study and, in the opinion of the investigator and confirmed by the sponsor, experienced a clinically important benefit from TAK-981 in combination with an assigned mAb may continue to receive TAK-981 or the combination in an extension phase of this study or will be given the opportunity to enroll in a separate open-label rollover study, if one is available, or have the possibility of using an individual patient investigational new drug to continue receiving both study drugs. Additionally, these patients should have no alternative therapeutic option and would be harmed without continued access.

6.5.5.1 Duration of Post-Study Access

Continued access to TAK-981 or the combination mAb for subjects may be terminated for those individuals who no longer benefit from TAK-981 or the combination (eg, they have completed the recommended course of therapy or their disease has resolved), that complete the protocol defined duration of treatment, for whom the benefit-risk no longer favors the individual, if TAK-981 ± mAb becomes available either commercially or via some other access mechanism, or when an alternative appropriate therapy becomes available. Post-study access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of TAK-981 or mezagitamab has been suspended or stopped by the sponsor, or the TAK-981 or mezagitamab can no longer be supplied. Daratumumab and hyaluronidase-fihj (Darzalex Faspro) is a commercially available product and post-study access would continue to be via commercial sources.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. Be willing and able to provide written informed consent for the study.
3. For patients with MM (for Phase 1b and Phase 2):
   a. A prior diagnosis of MM as defined by the IMWG criteria with documented disease progression (Appendix I [23,24]).
   b. Has measurable disease defined as one of the following:
      - Serum M-protein ≥0.5 g/dL (≥5 g/L).
      - Urine M-protein ≥200 mg/24 hours.
      - In patients without measurable M-protein in serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal.

c. Has undergone stem cell transplant or is considered transplant ineligible, and

- Patients with a history of autologous stem cell transplant are eligible if the transplant was > 100 days prior to study consent.

d. Has failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (eg, daratumumab, daratumumab and hyaluronidase-fihj, isatuximab) alone or in combination, and

e. Is either refractory, or intolerant to at least 1 IMiD (ie, lenalidomide or pomalidomide [thalidomide excluded]), at least 1 proteasome inhibitor (ie, bortezomib, ixazomib or carfilzomib), and refractory to at least 1 anti-CD38 antibody and who have demonstrated disease progression with the last therapy.

- Refractory myeloma is defined as disease that is nonresponsive while on therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of PD while on therapy.
- A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by a stem cell transplantation, consolidation, and maintenance is considered 1 line) [25].

4. Have a performance status of 0-2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
5. Have suitable venous access for safe drug administration and the study-required blood sampling, including PK and pharmacodynamic sampling.
6. Have adequate organ function as specified below at screening:

   a. Platelet count ≥75, 000 mm^3 (≥75 × 10^9/L); value of ≥50, 000 mm^3 (≥50 × 10^9/L) may be acceptable for patients with ≥50% bone marrow burden following discussion with the sponsor (platelet transfusion will be allowed > 3 days before assessment)

   b. Hemoglobin must be ≥8 g/dL. (RBC transfusion allowed ≥14 days before assessment).

   c. Absolute neutrophil count (ANC) ≥1000 mm^3 (≥1.0 × 10^9/L); value of ≥750 mm^3 (≥0.75 × 10^9/L) may be acceptable for patients with ≥50% bone marrow burden following discussion with the sponsor

   d. Estimated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/minute for patients with serum creatinine concentrations above the upper limit of normal range (ULN).

e. AST (glutamic oxaloacetic transaminase [GOT]) and ALT (GPT) ≤3.0 × ULN; bilirubin ≤1.5 × ULN. Patients with Gilbert's syndrome may have a bilirubin level >1.5 × ULN, per discussion between the investigator and the medical monitor.

7. Have recovered to Grade 1 or baseline from all toxicity associated with previous therapy or have the toxicity established as sequela.

   Note: except Neuropathy Grade ≤2, any grade alopecia, or bone marrow parameters [any of Grade 1 or 2 permitted if directly related to bone marrow involvement].

8. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 6 months after the last dose of drug in the combination. 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.)

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

   - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of drug in the combination, 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.)

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

7.2 Exclusion Criteria

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

1. Received treatment with systemic anticancer treatments within 14 days before the first dose of study drug or any investigational products (IPs) within 5 half-lives of the first dose of study drug, whichever is appropriate to last therapy received. (eg, non-IP IMiD, proteasome inhibitor, anti-CD38 mAb could be considered to be eligible if there is at least 14 days after last dose before first dose of study drug).

Note: Treatment with a single course of glucocorticoids (maximum dose of corticosteroids should not exceed the equivalent of 160 mg [for example, 40 mg/d for 4 days] of dexamethasone), 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.

2. Current participation in another interventional study, including other clinical trials with investigational agents (including investigational vaccines or investigational medical device for disease under study) within 4 weeks of the first dose of TAK-981 and throughout the duration of this trial.
3. Prior radiation therapy within 14 days of the first dose of TAK-981.

   Note: Prophylactic localized ("spot") radiation for areas of pain is allowed.
4. Major surgery within 4 weeks before C1D1. Patients should be fully recovered from any surgically related complications.

   Note: Kyphoplasty is not considered major surgery.
5. Plasmapheresis within 28 days of randomization.
6. Diagnosis of primary amyloidosis, Waldenström's disease, monoclonal gammopathy of undetermined significance or smoldering multiple myeloma (SMM) per IMWG criteria or standard diagnostic criteria, plasma cell leukemia (according to the World Health Organization [WHO] criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), myelodysplastic syndrome, or myeloproliferative syndrome.
7. With disease where the only measurable parameter is plasmacytoma.
8. 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.
9. Evidence of central nervous system involvement and/or meningeal involvement of MM exhibited during screening.
10. Known severe allergic or anaphylactic reactions to human recombinant proteins or excipients used in the TAK-981 formulation or the mAbs (such as daratumumab or daratumumab and hyaluronidase-fihj as per the prescribing information and for mezagitamab as outlined in the Mezagitamab IB).
11. History of treatment discontinuation due to treatment-related toxicity to the combination partner (daratumumab or daratumumab and hyaluronidase-fihj).
12. Prior treatment with more than 1 anti-CD38 antibody.

13. Chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1 second (FEV1) <50% of predicted normal; or diagnosis of moderate or persistent asthma within the last 2 years, or currently uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed); pulmonary fibrosis; or history of symptomatic bronchospasm. Note that FEV1 testing is required for patients with known or suspected COPD or asthma and patients must have a FEV1 ≥50% of predicted normal during screening.
14. Any concurrent or uncontrolled medical, comorbid, or psychiatric condition or disease that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.
15. History of HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
16. Systemic infection requiring systemic antibiotic therapy or other serious infection within 14 days before the first dose of TAK-981 or any agent in the combination.

    Note: Urinary tract infection is not considered a systemic infection.
17. 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.
18. Active or history of noninfectious pneumonitis that required steroids or a history of interstitial lung disease.
19. History of allogeneic tissue or solid organ transplant.
20. Receipt of any live vaccine (eg, varicella, pneumococcus) within 4 weeks of initiation of study treatment.
21. 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 F) or are strong P-glycoprotein (Pgp) inhibitors (Appendix G) at screening. To participate in this study, such patients should discontinue use of such agents for at least 2 weeks or 5 times the half-life (whichever is shorter) before receiving a dose of TAK-981.
22. Requires the use of drugs known to prolong the corrected QT interval (QTc) (during Phase 1b only) (Appendix I)
23. 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, uncontrolled hypertension despite appropriate medical therapy, ongoing symptomatic cardiac arrhythmias >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.

24. Baseline prolongation of the QT interval with Fridericia's correction method (QTcF) (eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes). If a machine reading is above this value, the ECG should be reviewed by a qualified reader and confirmed on a subsequent ECG.
25. 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.
26. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.
27. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a on Day 1 before first dose of TAK-981 study drug (Appendix A).

8.0 STUDY DRUG

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

8.1 Investigational Medicinal Products

8.1.1 TAK-981 Study Drug Administration

In Phase 1b each 28-day treatment cycle will consist of TAK-981 administered IV in one of the following schedules: (Also see Table 8.a and Table 8.b below):

- BIW on Days 1, 4, 8, 11, and 15 during Cycles 1 and 2, then once every 2 weeks during Cycles 3 through 6, followed by once every 4 weeks dosing, OR
- QW on Days 1, 8, 15, 22 during Cycles 1 and 2, then once every 2 weeks during Cycles 3 through 6, followed by once every 4 weeks dosing thereafter until PD.

In Phase 2, a schedule for TAK-981 will be selected for continued evaluation based on data from Phase 1b.

The initial Phase 1b starting dose of TAK-981 will be 60 mg. Dose escalation will begin with the BIW schedule.

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

For C1D1 only (Phase 1b and Phase 2), the mAb will be administered first (before the TAK-981 infusion). Starting at C1D8 onwards, TAK-981 will be administered before the mAb. On days in which both agents are given on the same visit day at least 1 hour should elapse between the completion of the first drug and the administration of the second drug. [Refer to Section 8.1.2 and Section 8.2.1 for more details.]

TAK-981 administration should occur in an area with resuscitating equipment and medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators readily available. Patient's vital signs (such as blood pressure, heart rate, and temperature) must be monitored before, during, at the end of administration of TAK-981, 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. Treatment must be stopped if the patient experience symptoms compatible with an infusion reaction of Grade 2 or greater. During C1, vital signs need to be monitored as above and up to 4 hours after the end of the infusion (for C1D1 up to 6 hours after the end of infusion). From C2 onwards, vital signs will be monitored immediately before the start of infusion and after the end of infusion and the patient can be discharged from the site per investigator discretion. The management of infusion reactions and CRS is detailed in Sections 8.11.1 and Section 8.11.2, respectively.

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

Dose administration should be performed on schedule; however, a dose delay of up to 4 days may occur because of such things as 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 8.9). At least 72 hours should lapse between consecutive doses of TAK-981. If the TAK-981 dose is delayed for the reasons above, the mAb would also be delayed. The reason for the delay will be documented in electronic data capture (EDC).

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.

8.1.1.1 TAK-981 Formulation

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

8.1.2 Mezagitamab (TAK-079)

After patients have received premedication, treatment with (Section 8.1.2.1) mezagitamab doses will be administered with syringes as SC injections up to a maximum volume of approximately 2 mL per injection (ie, 200 mg/2 mL) (refer to the pharmacy manual). The injection sites need to

be rotated, using the abdomen, thighs, arms, and upper buttock area. Time and anatomical site should be recorded for each SC injection.

Mezagitamab will be given by SC injection at a fixed dose of 600 mg in combination with TAK-981 (assigned dose and schedule; Section 8.1). During Phase 1b, 2 dosing schedules for TAK-981 will be evaluated: one utilizing a BIW schedule and the other a weekly schedule. The schedule for mezagitamab will be the same (Table 8.a and Table 8.b). Enrollment to the dose cohort will be sequential for the first cohort in each schedule and will begin with the BIW schedule. The pharmacodynamic, PK, safety, and efficacy data from these schedules will inform the dose and schedule to be used in Phase 2. Alternative schedules to that in Table 8.a or Table 8.b may be explored if recommended by the SMC.

Table 8.a Administration Schedule of TAK-981 and Mezagitamab (BIW TAK-981 Schedule)

Cycle	28-Day Cycles C1 and C2						28-Day Cycles C3 Through C6				28-Day Cycles C7 Through PD			
Day of Cycle	D1	D4	D8	D11	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Premedication	X		X		X	X	X		X		X			
TAK-981[a]	X	X	X	X	X		X		X		X			
Mezagitamab	X		X		X	X	X		X		X			

BIW: twice weekly; C: cycle; C1D1: Cycle 1, Day 1; D: day; PD: progressive disease.
[a] On C1D1, only the monoclonal antibody will be administered before TAK-981 administration.

Table 8.b Administration Schedule of TAK-981 and Mezagitamab (QW TAK-981 Schedule)

Cycle	28-Day Cycles C1 and C2				28-Day Cycles C3 Through C6				28-Day Cycles C7 Through PD			
Day of Cycle	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Premedication	X	X	X	X	X		X		X			
TAK-981[a]	X	X	X	X	X		X		X			
Mezagitamab	X	X	X	X	X		X		X			

C: cycle; C1D1: Cycle 1, Day 1; D: day; PD: progressive disease; QW: once weekly.
[a] On C1D1, only the monoclonal antibody will be administered before TAK-981 administration.

For C1D1 only, mezagitamab will be administered first (before TAK-981 infusion). Starting at C1D8 onwards, TAK-981 will be administered before the anti-CD38 mAb. On days on which both agents are given on the same visit day, at least 1 hour should elapse between the completion of the first drug and the administration of the second drug.

As an anti-CD38 mAb, systemic administration reactions are possible with mezagitamab; however, unlike daratumumab or daratumumab and hyaluronidase-fihj, none have been reported with the SC route of administration in patients with RRMM or newly diagnosed multiple myeloma (NDMM) to date (See mezagitamab current IB). Based on this, the rationale for dosing

mezagitamab before TAK-981 on C1D1 is to keep consistency with the TAK-981/ daratumumab and hyaluronidase-fihj combination and not for safety reasons.

8.1.2.1 Premedications

Before each injection, patients will receive the following premedication approximately 1 to 3 hours before the mezagitamab injection on each dosing day:

- Dexamethasone: 20 mg IV dose for the initial injection. Oral dexamethasone (20 mg) or an equivalent long-acting corticosteroid may be used before subsequent injections. May consider reducing the dose of dexamethasone to approximately 12 mg orally following the second dose before subsequent injections if no major systemic administration-related reactions reported. If the patient does not experience a major systemic administration-related reaction the physician may use their clinical judgement in discontinuing the administration of corticosteroids.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).

Note: For any patient with a history of COPD, consider premedication with montelukast 10 mg (or equivalent leukotriene inhibitor). Also consider prescribing postinfusion medications, such as short- and long-acting bronchodilators and inhaled corticosteroids. After the first 4 injections, if the patient experiences no major infusion reaction, these additional inhaled postinfusion medications may be discontinued.

The clinical site is responsible for sourcing any pre- and post-medications outlined in the protocol. Investigator may consider reducing, even discontinuing, predose and postdose medications, including corticosteroids after the first 3 mezagitamab injections, if the patient experiences no major systemic administration reaction. Additionally, dose reductions of pre-medications, specifically, dexamethasone, may be done at the physician's discretion based on reported dexamethasone-induced AEs.

8.1.2.2 Postmedication

Patients may receive low-dose methylprednisolone ≤20 mg (or an approximate equivalent such as dexamethasone ≤ 4 mg) for the prevention of delayed systemic administration reactions as clinically indicated after an injection.

Investigators may consider postinjection site care: such as corticosteroid cream topically to injection site(s) and apply ice locally for approximately 10 to 15 minutes. If used, report the corticosteroid cream as a concomitant medication.

8.1.2.3 Mezagitamab Formulation

Mezagitamab will be provided in vials of 100 mg/mL mezagitamab drug substance (refer to the pharmacy manual). The sponsor will provide mezagitamab.

8.2 Standard of Care Agents

8.2.1 Daratumumab and Hyaluronidase-fihj

The combination of TAK-981 and daratumumab and hyaluronidase-fihj will be evaluated. In Phase 1b Part 2, a safety lead-in of the combination of daratumumab and hyaluronidase-fihj with the dose and schedule of TAK-981 defined in Phase 1b Part 1 to confirm the RP2D of TAK-981 in combination with daratumumab and hyaluronidase-fihj. Daratumumab and hyaluronidase-fihj will be given at the recommended dose of 1800 mg subcutaneous injection according to the Darzalex Faspro US Prescribing Information (USPI). The dose will be administered SC as per the prescribing information [15]. The pharmacodynamic, PK, safety, and efficacy data from Phase 1b will inform the dose and schedule of TAK-981 to be used in Phase 2. Further information on the dose of TAK-981 is discussed in Section 8.1.1.

Table 8.c Administration Schedule TAK-981 and Daratumumab

Cycle	28-Day Cycles C1 and C2				28-Day Cycles C3 Through C6				28-Day Cycles C7 Through PD			
Day of Cycle	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Premedication	X	X	X	X	X		X		X			
TAK-981 [a]	The final schedule for TAK-981 in Phase 2 will be determined by the results from Phase 1b Part 1.											
Daratumumab and hyaluronidase- fihj	X	X	X	X	X		X		X			

C: cycle; C1D1: Cycle 1, Day 1; D: day; PD: progressive disease.
[a] On C1D1, only the monoclonal antibody will be administered before TAK-981 administration.

For C1D1 only, daratumumab and hyaluronidase-fihj will be administered first (before TAK-981 infusion). At least 4 hours should elapse between the completion of the administration of the daratumumab and hyaluronidase-fihj and the initiation of the TAK-981 infusion. Admission to the hospital or a clinical unit may be necessary for drug administration and research sample collection.

The rationale for dosing daratumumab and hyaluronidase-fihj before TAK-981 on C1D1 is that most of the infusion reactions due to daratumumab have been reported primarily during the first infusion with median time to onset of onset of 3.7 hours (range 9 minutes to 3.5 days). Of the systemic IRR reported, 87% occurred on the day of daratumumab and hyaluronidase-fihj administration [15]. The proportion of patients experiencing acute IRRs decreases with subsequent courses of daratumumab [15]. Although most daratumumab and hyaluronidase-fihj-related reactions are mild to moderate in severity, there is a theoretical risk that when combined with TAK-981 any such reactions could be more severe. Therefore, daratumumab and hyaluronidase-fihj is administered after premedication and before TAK-981 infusion on C1D1. Subsequent daratumumab and hyaluronidase-fihj injections are administered after TAK-981 infusion to facilitate PK/pharmacodynamic sampling.

- Starting at C1D8 onwards, TAK-981 will be administered before daratumumab and hyaluronidase-fihj. On days on which both agents are given on the same visit day at least 1 hour should elapse between the completion of TAK-981 infusion and the administration of daratumumab and hyaluronidase-fihj.
- For IRRs of any grade/severity, immediately interrupt the daratumumab and hyaluronidase-fihj infusion and manage symptoms. Management of IRRs may further require treatment discontinuation of daratumumab and hyaluronidase-fihj. Permanently discontinue the infusion in case of anaphylactic reactions or life-threatening IRRs and institute appropriate emergency care. Follow dose administration recommendations in the daratumumab and hyaluronidase-fihj prescribing information [15].

8.2.1.1 Vital Signs

Vital signs (blood pressure, heart rate, and temperature) should be checked before the start of the infusion, at the end of the infusion, as medically appropriate during the infusion based on patient symptomatology, and before discharge.

8.2.1.2 Premedications

Before each injection, patients will receive the following premedication approximately 1 to 3 hours before the daratumumab and hyaluronidase-fihj on each dosing day [15]:

- Methylprednisolone 100 mg (or approximate equivalent such as dexamethasone 20 mg) IV for the initial injection. Consider reducing the dose of methylprednisolone to 60 mg (or approximate equivalent such as dexamethasone 12 mg) orally or IV following the second dose of daratumumab and hyaluronidase-fihj before subsequent injections. If the patient does not experience a major systemic administration-related reaction after the physician may use their judgement in discontinuing the administration of corticosteroids.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).

Note: For any patient with a history of COPD, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids. Following the first 4 doses of daratumumab and hyaluronidase-fihj, consider discontinuing these additional post-medications, if the patient does not experience a major systemic administration-related reaction [15].

8.2.1.3 Postmedication

Administer methylprednisolone 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid such as dexamethasone 4 mg) orally for 2 days starting the day after the administration of daratumumab and hyaluronidase-fihj [15].

8.2.1.4 Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting daratumumab and hyaluronidase-fihj and continue for 3 months following the EOT [15].

The clinical site is responsible for sourcing daratumumab and hyaluronidase-fihj and any premedications and postmedications outlined in the protocol.

8.3 Definitions of DLT

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 [26]; except CRS which will be graded according to ASTCT Consensus Grading for CRS [27].

Patients will be monitored through all cycles of therapy for treatment-related toxicities. DLTs will be evaluated at the end of Cycle 1. Primarily, only toxicities that occur during Cycle 1 will be used for the purposes of defining DLT for future cohort expansion or dose modification decisions. If noncompliance with protocol defined requirements (eg, antiviral prophylaxis) results in toxicities of ≥ Grade 3, these toxicities should not qualify as DLTs. Use of platelet transfusions or growth factors to manage AEs that may represent DLTs, but are not yet clearly a DLT, should be discussed with the sponsor. TEAEs that are clearly due to extraneous causes will not be defined as DLTs.

A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related TAK-981:

1. Any Grade 5 AE.
2. Hematologic toxicity, clearly unrelated to the underlying disease are defined as follows:
   a. Nonfebrile Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L; ANC <500 cells/mm^3) lasting more than 7 consecutive days.
   b. Febrile neutropenia: Grade ≥3 neutropenia (ANC $<1 \times 10^9$/L; ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as a body temperature ≥38.5°C.
   c. Grade 4 thrombocytopenia.
   d. Grade 3 thrombocytopenia with clinically significant bleeding where clinically significant bleeding requires a RBC transfusion.
   e. Grade 4 anemia, unexplained by the underlying disease.
3. Nonhematologic toxicity of Grade 3 or higher clearly unrelated to the underlying disease, with the exception of:
   a. Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs within 7 days.
   b. Grade 3 endocrine disorders, including adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, hypopituitarism, and type 1 diabetes mellitus, that are managed with or without therapy and the patient is asymptomatic.

c. Grade ≥3 IRR that resolves within 6 hours with appropriate clinical management. Note: C1D1 IRRs due to the mAb will not be considered a DLT if the IRR occurred before TAK-981 administration and the patient did not receive TAK-981; the patient will not be considered DLT-evaluable and will be replaced.

d. Grade ≥3 CRS that resolves to Grade ≤1 48 hours without end-organ damage; graded according to ASTCT Consensus Grading for CRS [27].

e. 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.

f. 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.

g. 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 serotonin receptor subtype 3 (5-HT3) antagonist and a corticosteroid given in standard doses and according to standard schedules).

h. Grade 3 diarrhea that can be controlled to <Grade 3 in ≤3 days with appropriate treatment.

i. Grade 3 rash lasting ≤72 hours after treatment that includes topical steroid treatment, oral antihistamines, and pulse oral steroids (if necessary).

4. Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug (TAK-981) and dose-limiting (dose reduction or discontinuation).
5. 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.
6. Missed >1 planned doses of TAK-981 or ≥1 planned dose of mAb in Cycle 1 due to treatment-related AEs.

8.4 Definition of DLT-Evaluable Patients

Patients assigned to a particular dose cohort in Phase 1b are considered evaluable for assessment of a DLT if either of the following criteria are met during the DLT assessment period of 28 days following the first dose of treatment (Cycle1):

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

  OR

- The patient completed all Cycle 1 doses of mAb and at least 75% of planned TAK-981 doses.

For the Phase 1b part of the study, patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above,

will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

8.5 Dose Escalation Rules

In the Phase 1b portion of the study, only TAK-981 will be escalated/de-escalated. Each individual mAb is administered at its established dose. The first part of the Phase 1b will determine the dose and schedule of TAK-981 in combination with a fixed dose and schedule of mezagitamab for expansion. The second part of the Phase 1b will determine the dose of TAK-981 for the combination with daratumumab and hyaluronidase-fihj.

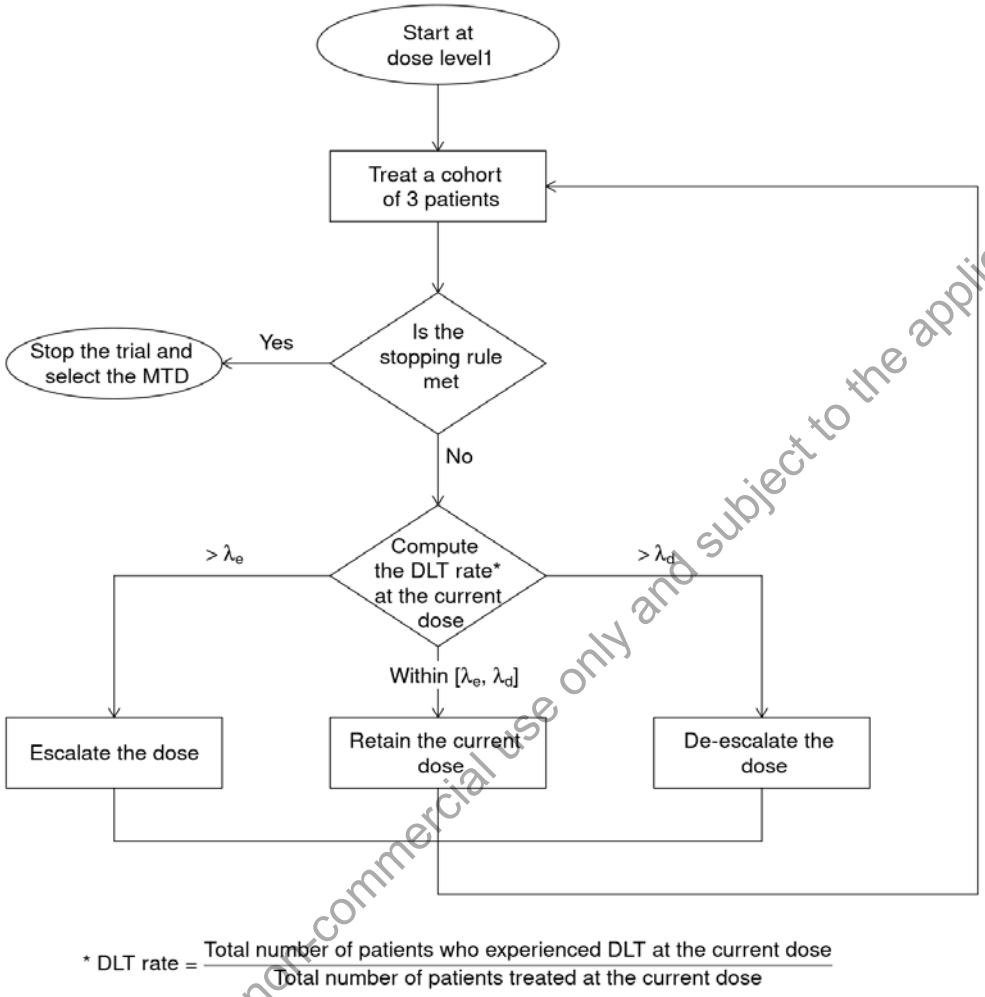
In the Phase 1b Part 1, the starting dose level of TAK-981 will be 60 mg which is 1 dose level below the monotherapy dose that has cleared the DLT period in the ongoing FIH single agent study (Study TAK-981-1002). The following dose levels of TAK-981 will be potentially considered: 60 , 90, and 120 mg, (Table 8.d). TAK-981 cannot be escalated above the MTD defined in the FIH study. Evaluation of lower or intermediate dose levels and alternative schedules are permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of toxicity, exposure, or pharmacodynamics of TAK-981.

Dose escalation will follow an iBOIN design [28]. Each schedule will be evaluated separately.

Approximately 3 patients will be enrolled in the first cohort. The decision to escalate or de-escalate the dose of TAK-981 will be based the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the iBOIN .model and on the cumulative DLT rate. The target DLT rate for this study is 0.3. The dose escalation and de-escalation rules for TAK-981 are as follows (Figure 8.a).

1. If the observed DLT rate at the current dose is $< \lambda_e$, escalate the dose to the next higher dose level;
2. If the observed DLT rate at the current dose is $> \lambda_d$, de-escalate the dose to the next lower dose level;
3. Otherwise, stay at the current dose.

Figure 8.a Phase 1b Dose Escalation Schema



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

It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate dose escalation for each dosing schedule of TAK-981. For each cohort of patients enrolled at a given dose level, the observed DLT rate will be calculated for that dose level. If the observed DLT rate at the current dose is $< \lambda_e$, the next cohort of patients will be treated at the next higher dose level; if it is $> \lambda_d$, the next cohort of patients will be treated at the next lower dose level. The values for λ_e and λ_d vary with dose level and the number of patients treated on a dose. The boundary guiding the number of patients treated at the current dose is displayed in Appendix H in which the operating characteristics of the iBOIN design based on 1000 simulations of each scenario are presented.

Alternative dosing schedules for TAK-981 will be explored. The dose escalation for different TAK-981 schedules will be evaluated separately.

Once the RP2D is defined for the combination with mezagitamab, the TAK-981 dose and schedule will be determined using the same methodology as described above. The starting dose and schedule of TAK-981 for the combination with daratumumab and hyaluronidase-fihj will be 1 dose level below the RP2D of TAK-981 defined in combination with mezagitamab (RP2D-1). The dose of TAK-981 will not be escalated beyond the RP2D determined for the combination with mezagitamab.

Approximately 3 patients will be enrolled in the combination. The decision to escalate or de-escalate the dose of TAK-981 will be based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the iBOIN design in which the prior information on the dose-toxicity relationship from the Phase 1b Part 1 for the dose escalation of combination with mezagitamab.

It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate the dose of TAK-981 in combinations with daratumumab and hyaluronidase-fihj using similar approach for dose escalation of TAK-981 in combination with mezagitamab.

Dose escalation and cohort expansion decisions will be determined by the SMC. The SMC will review the Cycle 1 safety of all treated patients and will take into consideration the pattern of AEs beyond the DLT window across all patients enrolled and make decisions regarding dose escalation. In addition, the available PK and pharmacodynamic information will also be evaluated to support the dose escalation.

The planned dose levels for the Phase 1b portion of TAK-981 are shown in Table 8.d.

Table 8.d Planned Dose Levels

Dose Level	Dose (Unit) [a]
-2	25 mg
-1	40 mg
1	60 mg
2	90 mg
3	120 mg

[a] Dose levels indicate the maximum dose escalation per step. Intermediate dose levels can be used based on clinical observations and on data from other TAK-981 studies.

8.6 Intrapatient Dose Escalation

Patients who have tolerated treatment at the initially assigned dose may have their doses of TAK-981 increased to the RP2D once it has been determined. After discussion with the sponsor, at the investigators' discretion, patients may be switched to the RP2D in a stepwise process, including intermediate dose levels identified at the investigator's discretion.

8.7 Dose Modification Guidelines for Phase 1b Dose Escalation and Phase 2 Expansion Cohorts

Toxicities should be attributed, whenever possible, to a specific drug (TAK-981, mezagitamab, or daratumumab and hyaluronidase-fihj, as applicable based on the assigned regimen) so that dose modification can be made rationally. Reduction of a single agent and not others is appropriate if toxicity is considered to be related primary to one of the agents. If multiple toxicities are attributed to an individual agent dose adjustments should be made according to the guidelines for the most severe toxicity. Dose modification are 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). See details for managing specific AEs in Section 8.11.

8.7.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

A treatment cycle in this study is 28 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.

Before starting a new treatment cycle, TAK-981/mAb-related AEs or laboratory abnormalities must have returned to Grade ≤1 or baseline (unless otherwise specified) or to a level considered acceptable by the physician if the toxicity is a nonhematologic one. If the patient fails to meet the criteria cited above for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. When the agents are held based on the listed criteria, clinical and laboratory reevaluations should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed. At the end of that week, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor. Note: 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 represents a DLT.

If the dose of TAK-981 causes a delay in the initiation of a cycle, all drugs in the combination are also delayed. Further, if a dose is delayed (interrupted), then the dates of all subsequent doses and assessments must be adjusted accordingly. Specific issues related to this approach can be discussed with the Takeda project clinician/designee.

8.7.2 Criteria for Dose Interruption or Dose Reduction During a Cycle

Toxicities should be attributed, whenever possible, to a specific drug (TAK-981, mezagitamab, or daratumumab and hyaluronidase-fihj as applicable based on the assigned regimen) so that dose interruption or reduction can be made rationally. Reduction of a single agent and not others is appropriate if toxicity is considered to be related primary to 1 of the agents. All toxicities that

occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-981, a mAb, or the combination may continue study treatment with the same dose, may have the treatment held, or may be permanently discontinued from the study. Patients who have study drugs held because of treatment-related or possibly related AEs should resume study drug treatment according to the dose modification guidelines below.

8.7.3 Dose Modification and Discontinuation Criteria for TAK-981

8.7.3.1 Dose Modification Criteria for TAK-981

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

In the BIW schedule, if TAK-981 alone or in combination with the mAb cannot be administered within a cycle in a 48-hour window, because of an AE, the dose will be missed, and the patient will be scheduled for the next administration per SOE. In the QW schedule a window of 72-hours is permitted. In these cases, the subsequent dose will be administered as planned.

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

In the Phase 1b portion of the study, dose reductions of TAK-981 are not permitted in Cycle 1 unless the patient experiences a DLT attributed to TAK-981. DLTs are defined in Section 8.3. Patients experiencing a DLT in Cycle 1 may continue in the study upon resolution of the toxicity; however, a dose reduction by at least 1 dose level of TAK-981 should be considered based on the toxicity and discussion between investigator and sponsor.

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

Table 8.f 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).

Table 8.f Dose Adjustments for Hematologic Toxicities

Criteria	Action
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN- 75.0 × 10^9 cells/L)	Continue TAK-981 at the same dose level.
Grade 2 (PLT <75.0 - 50.0 × 10^9 cells/L)	Continue TAK-981 at the same dose level.
Grade 3 (PLT <50.0 - 25.0 × 10^9 cells/L) without bleeding	Withhold dose until resolved to Grade ≤1 or baseline, then: If resolved in ≤7 days, resume treatment at the same dose level. If resolved in >7 days, resume treatment at the previous safe lower dose level (ie, reduce by 1 dose level).
Grade 4 (PLT <25.0 × 10^9 cells/L) without bleeding	Withhold dose until resolved to Grade ≤1 or baseline, then if resolved in ≤7 days, resume treatment at the same dose level, if resolved in >7 days, then resume treatment at the previous safe lower dose level.
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; C; cycle; LLN: lower limit of normal; PLT: platelets.

8.7.3.2 Discontinuation Criteria for 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 (+7) days of the last administration of TAK-981 and before the start of subsequent anticancer therapy.

8.7.4 Dose Modification and Discontinuation Criteria for Mezagitamab

All toxicities that occur during the study will be actively managed following medical standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to mezagitamab may continue study treatment with the same dose, may have mezagitamab treatment held, or may be permanently discontinued from the study, depending on the nature and severity of the AE and whether it is the first occurrence, or it is recurrent. TEAEs that are not

attributed by the investigator to the mezagitamab may be treated as per local standard of care; dose modifications, interruptions, and permanent discontinuations may be discussed upfront with the medical monitor. Any dose interruption of more than 28 days due to toxicity may result in permanent discontinuation of mezagitamab.

Table 8.g provides general dose modification recommendations. If there are transient laboratory abnormalities that, per investigator assessment, are not clinically significant or drug-related, continuation of therapy without dose modification is permissible upon discussion with the sponsor. Toxicity is managed using dose interruptions, including missed doses, as is standard with administration of mAbs as a means to reduce dose intensity [14,29,30].

Table 8.g Dose Modification Recommendations for Mezagitamab Toxicities

Criteria	Action
Grade 1 AEs	No dose interruptions
Grade 2 AEs	• Treat according to local practice. The decision whether to hold treatment or to continue it at the same dose is made at the discretion of the investigator. • Patients with 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, then restarted at the same dose.
Grade 3 AEs	• Patients with Grade 3 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline, then resume treatment at the same dose level (see Section 8.11 for AEs of short duration and/or those that respond to medical management). • Grade ≥3 thrombocytopenia with bleeding should result in a dose interruption until the AE resolves to Grade ≤1 or baseline, then resume at the same dose
Grade 4 life-threatening AEs	• Patients with Grade 4 AEs non-hematologic toxicity considered related to study treatment should permanently discontinue treatment. Grade 4 hematologic toxicity should result in study treatment interruption until the AE resolves to Grade ≤1 or baseline, then resume at the same dose.
AEs of all grades	• If mezagitamab administration does not commence within the prespecified window (see Appendix A) of the scheduled administration date, then the dose will be considered a missed dose (see Table 8.h). Administration may resume at the next planned dosing date upon recovery as described previously.

AE: adverse event.

If an initial dose interruption does not provide sufficient relief, the dose of mezagitamab should be considered for permanent discontinuation.

Table 8.h Mezagitamab-Related Toxicity Management

Dose Frequency	Dose Missed	Dose Resumption
Weekly	>3 days	Skip dose, move to next planned weekly dose.
Every 2 weeks	>7 days	Skip dose, move to next planned every 2 week dose.
Every 4 weeks	>21 days	Skip dose, move to next planned every 4 week dose.

A mezagitamab dose held for more than 3 days from the per-protocol administration date for any reason other than AEs should be brought to the attention of the sponsor/designee as soon as possible. Patients missing ≥3 consecutive planned doses of mezagitamab for reasons other than AEs should be withdrawn from treatment, unless, upon consultation with the sponsor/designee and review of safety and efficacy, continuation is agreed upon. A missed dose will not be made up. Doses of mezagitamab to be administered every 4 weeks may be delayed (interrupted) up to 4 weeks (see Table 8.h). If a dose is delayed (interrupted), then the dates of all subsequent doses and assessments must be adjusted accordingly. Any AE deemed to be related to mezagitamab that requires a dose delay (interruption) of more than 28 days should result in permanent discontinuation of mezagitamab, unless both the investigator and the sponsor study clinician believe the patient is deriving clinical benefit.

8.7.5 Dose Modification and Discontinuation Criteria for Daratumumab and Hyaluronidase-fihj

All toxicities that occur during the study will be actively managed following medical standard of care unless otherwise specified in the protocol. Toxicities attributed to daratumumab and hyaluronidase-fihj, as applicable, should be managed according to the relevant guidelines in the respective product information. Toxicity is managed using dose interruptions, including missed doses, as is standard with administration of mAbs as a means to reduce dose intensity [15].

8.7.6 COVID-19

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

- The infection must have resolved without ongoing clinical sequalae.
- There must be 2 sequential negative SARS-CoV-2 tests 12 hours apart.
- The patient must be asymptomatic and the investigator believes, with agreement of the sponsor, that the patient would benefit from resuming study treatment.

8.8 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

1. Radiation therapy for the disease under study. (Note that, in general, the requirement for local radiation therapy indicates PD; "spot" radiation for areas of pain is permitted after agreement with the sponsor study clinician/designee and after PD is ruled out).
2. Any antineoplastic treatment with activity against the disease under study, other than that described in this study.
3. Any investigational agent other than TAK-981 or mezagitamab, including agents that are commercially available for indications other than the disease under study that are under investigation for the treatment of the disease under study.
4. Concomitant corticosteroid administration of >10 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 for TEAE management eg, exacerbations of respiratory tract disorders or for acute control of emerging tumor pain.
5. In Phase 1b, initiation of prophylactic use of myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor) 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. Use of growth factors before confirmation of DLT will result in the event being defined as a DLT.
6. In Phase 1b, platelet transfusion in the first cycle before confirmation of DLT, given to manage patients who experience Grade 4 thrombocytopenia if clinically indicated, will result in the event being defined as a DLT.
7. Initiation of new erythropoietin therapy is not allowed during the first cycle. (Note Permitted Medication below regarding patients already on chronic erythropoietin).

8.8.1 Excluded Concomitant Medications and Procedures for TAK-981

The following medications and procedures are prohibited during the study:

1. 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.
2. Strong inhibitors of Pgp (see list in Appendix G).
3. Drugs known to prolong QTc interval (see list in Appendix I).

4. For patients enrolled in Phase 1b, any vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs.

8.8.2 Excluded Concomitant Medications and Procedures for Monoclonal Antibodies

For important drug interactions involving daratumumab, refer to the prescribing information [14,15].

8.9 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care will be available to patients as necessary. During study treatment, all blood products and concomitant medications, prescription and over-the-counter medications including influenza vaccines, received as of the first study drug administration until 30 days after the final dose or before initiation of new anticancer therapy (whichever comes first) will be recorded in the designated electronic case report form (eCRF). Initiation of a CoV-2 vaccination and/or COVID-19 treatment should be discussed with the sponsor/designee. 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 TAK-981 or any of the mAbs:

1. 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 [31]. If bisphosphonate therapy was not started before the study commenced, it should be initiated as soon as clinically indicated.
2. Unless there is a clinical contraindication, prophylactic herpes zoster antiviral prophylaxis therapy is required for all patients while receiving daratumumab and hyaluronidase-fihj as per relevant product information or standard of care/local practice [15]. For patients receiving other mAbs, prophylaxis can be started at investigator's discretion.
3. Agents involved in this study may cause fetal harm when administered to a pregnant woman. Please follow relevant product information instructions for daratumumab and hyaluronidase-fihj, as well instructions in Section 8.10.
4. Concomitant corticosteroid administration given as treatment or prophylaxis for IRRs, as premedication for administration of certain blood products or short courses for exacerbations of respiratory tract disorders or for acute control of emerging tumor pain. Doses of > 10 mg of prednisone or equivalent should be used with caution given its antimyeloma effect.
5. Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor). Their use should follow the product label, published guidelines, and institutional practice [32]. (Note: Excluded medication list for use during Cycle 1 of Phase 1b).

6. Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin.
7. Transfusions with RBCs and platelets as clinically indicated; however, use during Phase 1b Cycle 1 may represent a DLT.
8. Localized radiation for pain management for osteolytic lesions.
9. Topical or inhaled steroids and short-acting β2 adrenergic receptor agonists (eg, for the treatment of asthma) are permitted.
10. Nonresorbable corticosteroids (eg, budesonide).
11. Plasmapheresis.
12. Narrow therapeutic range Pgp substrates such as digoxin or dabigatran may be used with caution, and patients required use of these drugs will be closely monitored.
13. Trimethoprim-sulfamethoxazole prophylaxis for pneumocystis is permitted at the physician's discretion
14. Supportive measures consistent with optimal patient care to prevent and actively manage AEs or comorbidity may be given throughout the study treatment period. 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.
15. COVID-19 vaccination is generally allowed for patients enrolled in the study with the exception of live attenuated vaccines which must be completed at least 4 weeks prior to treatment initiation. COVID-19 vaccination should follow local guidances and regulations. Ideally, patients will have completed vaccination prior to treatment initiation. For patients enrolled in Phase 1b, vaccination during Cycle 1 is not permitted as this may confound the evaluation of safety and the determination of DLTs. Vaccination should be avoided within ±3 days of TAK-981 administration and should be administered after the last dose of TAK-981 of a given cycle; study treatment may be delayed for up to 7 days to accommodate a vaccine dose administration after discussion with the sponsor. Vaccination should be captured as a concomitant medication.

8.10 Precautions and Restrictions

It is not known what effects TAK-981 or the mAbs have on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below (see also Appendix E for acceptable methods of contraception).

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the informed consent form (ICF) through 6 months after the last dose of drug in the combination, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of drug in the combination, 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.

8.11 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, granulocyte-colony stimulating factor, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology/American Society of Clinical Oncology guidelines or local institutional practice. If dose alterations are necessary as a result of the events detailed below, refer to Section 8.6.

In the sections below guidance for the management of some expected AEs based on observations in nonclinical toxicology or other AEs that have not been substantiated in these experiments but that could be expected because of the MOA of TAK-981 and mezagitamab, and warnings and precautions in the daratumumab and hyaluronidase-fihj product label [15]. This guidance is not expected to replace investigator judgment in the management of AEs.

8.11.1 IRRs

In all cases, patients should be treated in a location with resuscitation equipment and where medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and

bronchodilators are readily available. Patients' vital signs must be monitored before, during, and at the end of administration of TAK-981 as well as before and after the daratumumab and hyaluronidase-fihj injections as per the assigned cohort. Treatment must be stopped immediately if the patient experiences symptoms compatible with an IRRs.

Depending on the severity of the potential IRRs observed, the TAK-981 infusion rate may be decreased by 50% or discontinued. The relevant mAb administration may also need to be interrupted (daratumumab and hyaluronidase-fihj and possibly mezagitamab) as per the prescribing information [15]. The patient should be promptly treated for signs and symptoms with antihistamines and corticosteroids at the investigator's discretion. Concomitant medications administered as treatment for IRRs will be recorded in the eCRF.

8.11.1.1 TAK-981

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 serious adverse event (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.

8.11.1.2 Monoclonal Antibodies

IRRs have been reported with the selected mAbs at different rates and different severities.

- **Daratumumab and hyaluronidase-fihj:** systemic hypersensitivity reactions have been reported in approximately 11% of patients (37% of patients who received the IV formulation of daratumumab) overall [14,15]. Reactions primarily occur with the first injection with a median time to onset of 3.7 hours (range 9 minutes to 3.5 days). Nearly all reactions (87%) occurred on the day of daratumumab and hyaluronidase-fihj administration. Delayed systemic administration related reactions have also been reported. Severe reactions included hypoxia, dyspnea, and hypertension. Other signs and symptoms may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing as well as anaphylactic reactions, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Premedication is required (see Section 8.2.1). Monitor patients for systemic IRRs, especially during and following the first and second injections. For anaphylactic or life-threatening reactions, immediately and permanently discontinue daratumumab and hyaluronidase-fihj and treat as medically appropriate [15]. Consider administering corticosteroids and other medications after the administration of daratumumab

and hyaluronidase-fihj depending on medical judgement to minimize the risk of delayed systemic IRRs.

- **Mezagitamab:** Based on the MOA of mezagitamab and qualitative similarities to that of daratumumab, systemic administration-related reactions and CRS are possible. (Mezagitamab IB) Generally, symptoms of hypersensitivity range from mild skin rash to more severe reactions, including the following: wheezing, hypotension, poor perfusion, and respiratory arrest. Nonanaphylactic clinical hypersensitivity can occur within the first hour, but delayed responses have also been reported in the literature with other biologic agents [33]. It is noteworthy however, that as of the current IB, no IRRs have been documented with mezagitamab in patients in the RRMM, NDMM, or SLE studies (each population receives preinjection medications of an antipyretic and an antihistamine, while patients with RRMM and NDMM also receive low-dose dexamethasone). Refer to the Mezagitamab IB for additional information and see Section 8.1.2.1 for premedications.

8.11.2 CRS

CRS should be diagnosed and managed following institutional guidelines and graded following ASTCT Consensus Grading for CRS [27]. CRS may occur after the first infusion of the drug because of a high level of activation of the immune system and engagement and proliferation of T cells that can result in increased cytokine release. The CRS hallmark is fever. CRS is a disorder that may also be characterized by tachypnea, headache, tachycardia, hypotension, chills, fatigue, nausea and/or vomiting, rash, urticaria, and/or hypoxia caused by the release of cytokines [34,35]. CRS should be diagnosed and managed following institutional guidelines. Investigators should try to differentiate CRS syndrome from other IRRs. Patients who develop severe CRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

Recommendations for management of CRS are shown in Section 8.11.2 and can be implemented at the investigator's discretion.

8.11.2.1 TAK-981

Acute and transient mild increased body temperature and reactive increased heart rate without changes in blood pressure with onset between 6 and 24 hours postinfusion were observed in nonclinical studies. These acute toxicology findings shortly after the infusion and the MOA of stimulation of IFN-I signaling raise the possibility of IRRs/CRS even with a negative cytokine release assay. Mild to moderate CRS have been reported in clinical studies with TAK-981. Refer to the TAK-981 IB for additional information.

8.11.2.2 Mezagitamab

CRS represents an important IRR associated with the use of mAbs. Nonclinical studies suggest that mezagitamab is unlikely to cause cytokine release due to cell activation; however, mezagitamab is a cell-depleting antibody so it could cause cytokine release due to cell lysis. Infusion-related reactions including hypersensitivity reactions and CRS have been reported with

other biologic agents, therefore, similar AEs may be seen with mezagitamab. The limited clinical data in healthy subjects given mezagitamab is insufficient to fully characterize infusion reactions (hypersensitivity reactions, CRS) associated with mezagitamab administration. However, as noted with IRR as per the mezagitamab IB, no CRS has been formally diagnosed in the RRMM, NDMM, or SLE studies. Refer to the Mezagitamab IB for additional information.

8.11.2.3 CRS Management

Patients should be monitored during and after infusion as defined in the protocol and should be considered clinically stable by the investigator or designee before discharge.

In all cases, patients should be treated in a location with resuscitation equipment and where medications such as antihistamines, acetaminophen, corticosteroids, epinephrine, and bronchodilators are readily available. Patients' vital signs must be monitored before, during, and at the end of administration of TAK-981 and after last drug in the combination. Treatment must be stopped immediately if the patient experiences symptoms compatible with an IRR or CRS.

Depending on the severity of the potential IRRs observed, the TAK-981 infusion rate may be decreased by 50% or discontinued. The relevant mAb administration may also need to be interrupted (daratumumab and hyaluronidase-fihj and possibly mezagitamab). The patient promptly treated for signs and symptoms with antihistamines and corticosteroids at the investigator's discretion. Concomitant medications administered as treatment for IRRs will be recorded in the eCRF.

Table 8.i CRS Management Recommendations and TAK-981 Dose Modifications

ASTCT Consensus Grade	CRS Management Recommendations and TAK-981 Dose Modifications
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 all agents in the combination until recovers to Grade ≤1. • Once recovered, restart TAK-981 at the same dose level; restart the monoclonal antibody at the same dose A maximum of 2 consecutive TAK-981 doses can be skipped; otherwise TAK-981 must be permanently discontinued.

Table 8.i CRS Management Recommendations and TAK-981 Dose Modifications

ASTCT Consensus Grade	CRS Management Recommendations and TAK-981 Dose Modifications
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 methyl prednisone. • Vasopressors as needed. • Supplemental oxygen as needed for hypoxia (including high-flow O2 and CPAP). • Transfer to ICU. *TAK-981 dosing* • Withhold all agents in the combination until recovers to Grade ≤1. Restart the monoclonal antibody at the same dose. • 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)	As per Grade 3 and: • Substitute dexamethasone with methyl prednisone 1 g IV per day. • Mechanical ventilation. *TAK-981 dosing* • Permanently discontinue TAK-981. Per Section 6.5.2, once TAK-981 is permanently discontinued, the monoclonal antibody is also discontinued.

ASTCT: American Society for Transplantation and Cellular Therapy; BiPAP: bilevel positive airway pressure; C: cycle; CPAP: continuous positive airway pressure; CRS: cytokine release syndrome; ICU: intensive care unit; IV: intravenous; O2: supplemental oxygen.

ASTCT consensus grade adapted from Lee et. al. 2019 [27]; CRS management recommendations are adapted from Neelapu et al. 2018 [36] 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.

8.11.3 Anemia, Thrombocytopenia, and Neutropenia

Hematologic toxicity is an overlapping toxicity between TAK-981 and the selected mAbs, though the severity of hematologic toxicity may vary between the mAbs ([14], Mezagitamab IB). Treatment decisions will be based on patient platelet counts; eg low platelet counts (Grade 4) should cause scheduled treatment to be postponed or to be permanently discontinued if recovery is delayed. Platelet transfusion, evaluation of coagulation parameters, and the Coombs test parameters (namely for patients receiving anti-CD38 mAbs) on the basis of signs and symptoms per investigator discretion are recommended. Please refer to Table 8.f, Table 8.g, and the relevant product labels for dose delay and reduction recommendations for hematologic toxicities as relevant to the assigned regimen. Complete blood counts should be monitored periodically during treatment.

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. Consider holding the relevant mAb to allow for cytopenia recovery.

- Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBCs or platelet) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/thrombocytopenia at the discretion of the investigator per standard clinical practice.
- Use of myeloid growth factor (eg, granulocyte-colony stimulating factor) support to treat Grade ≥3 neutropenia and/or febrile neutropenia is recommended per regional guidelines or local institutional practice; prophylaxis is permitted per regional guidelines or local institutional practice.

8.11.4 Infusion Site Care

8.11.4.1 TAK-981

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

8.11.4.2 Mezagitamab

Rotate injection sites for successive injections. Never inject either mAb into areas where the skin is red, bruised, tender, hard or areas where there are scars. Pause or slow down delivery rate if the patient experiences pain; change sites as necessary. Prophylactic postinjection site care is allowed such as corticosteroid cream topically to injection site(s) and apply ice locally for

approximately 10 to 15 minutes (report the corticosteroid cream as a concomitant medication). Additional injection site care may be provided on the basis of signs and symptoms per investigator discretion (report any actions as a concomitant medication). If necessary management may include discontinuation of the mAb.

With mezagitamab, injection site reactions have been very limited (0.22%), only mild, transient, and primarily erythema or tenderness with palpitation. Refer to the Mezagitamab IB for additional information.

8.11.4.3 Daratumumab and Hyaluronidase-fihj

Injection -site reactions have occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent injection site reaction was injection site erythema. Onset of local reactions occurred a median of 7 minutes (range 0-4.7 days) after starting administration of daratumumab and hyaluronidase-fihj. Monitor for local reactions and consider symptomatic management [15].

8.11.5 Nausea and Vomiting

Phase 1b part of the 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.

8.11.6 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.

8.11.7 Interference with Serologic Testing

Anti-CD38 mAbs, such as daratumumab, daratumumab and hyaluronidase-fihj, and isatuximab, have been reported to bind to CD38 on RBC and result in a positive indirect coombs test, which may persist for up to 6 months [14,15,37]. The determination of a patient's ABO and Rh blood type are not impacted, but the RBC binding may mask detection of antibodies to minor antigens in the patient's serum [14,15,37,38]. It is possible mezagitamab may affect the results of these blood tests, this is being evaluated. Until those tests are known, it is recommended that baseline type and serological screening be established before starting study treatment. This information may be available historically depending on previous exposure to a mAb. Patients should keep these results in case future transfusions are needed. Blood transfusion centers should also be informed of this interference with serological testing as necessary [38].

8.11.8 ADA Interactions

As with all therapeutic proteins, there is a potential for immunogenicity to the selected mAbs in this study [14,15]. Refer to the Mezagitamab IB and the daratumumab and hyaluronidase fihj product information for additional information.

8.12 Blinding and Unblinding

This is an open-label study.

8.13 Description of Study drugs

8.13.1 TAK-981

TAK-981 drug product has been developed as an injection, for IV use (solution for infusion). [redacted] It is packaged in a glass vial 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 manual 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 TAK-981 IB.

8.13.1.1 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.

8.13.1.2 Packaging and Labeling

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

8.13.1.3 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.

8.13.2 Mezagitamab

Mezagitamab is a full-length, human IgG1 mAb directed against human CD38. [redacted]

The strength of the Mezagitamab drug product for SC use in this study is 100 mg Mezagitamab in 1 mL (100 mg/mL). Mezagitamab drug product is supplied in aseptically filled, single-use, clear, type I, borosilicate glass vials with fluoropolymer-coated butyl rubber stoppers and aluminum crimp seals with flip-off caps.

8.13.2.1 Preparation, Reconstitution, and Dispensation

Refer to the pharmacy manual for detailed instructions regarding the preparation of mezagitamab study supply.

Mezagitamab is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling mezagitamab.

8.13.2.2 Packaging and Labeling

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

8.13.2.3 Storage and Handling

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained for all used and unused mezagitamab 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.

Mezagitamab must be stored under the conditions specified on the label and remain in the original container until dispensed (see the pharmacy manual for additional information). Detailed dosage preparation instructions are provided in the Directions for Use section of the pharmacy manual. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed.

8.13.3 Non-investigational Monoclonal Antibody

8.13.3.1 Daratumumab and Hyaluronidase-fihj

Daratumumab and hyaluronidase-fihj will be procured by the site from commercial sources. Additional details are provided in the package insert [15].

Daratumumab and hyaluronidase-fihj vials should be stored at temperatures in accordance with the instructions provided in the manufacturer's product label.

8.14 Investigational Drug Assignment and Dispensing Procedures: TAK-981 and Mezagitamab

Patients will be assigned using an integrated voice response system/interactive web response system (IVRS/IWRS) accessible 24 hours a day to authorized users. At screening, the site will contact the IVRS/IWRS to register the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information. At drug dispensing visits, the investigator or designee will contact the IVRS/IWRS to request study medication assignments for a subject. Medication ID (MED ID) numbers of the study medications to be dispensed will be assigned by the IVRS/IWRS. Documentation of the IVRS/IWRS assigned MED IDs should be included in the source documents.

8.15 Other Protocol-Specified Materials

TAK-981 and mezagitamab will be supplied by the sponsor. No other drugs or ancillary materials are supplied by sponsor for use in this trial.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the 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 (IRT) provider and the contract research organization (CRO), may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

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

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Treatment Group Assignments

The study uses a non-randomized, uncontrolled, parallel arm design. All patients will receive open-label treatment with TAK-981, daratumumab and hyaluronidase-fihj, or mezagitamab as indicated in the respectively assigned treatment cohort and Phase of the study. Patients will be assigned to a treatment regimen in a nonrandomized manner based upon the investigator's judgment and the recruitment status of the available cohort as communicated by the sponsor. Once a treatment cohort has been fully enrolled, further enrollment will be stopped to that combination unless a decision has been made to expand the cohort for a better understanding of efficacy, safety, PK, or pharmacodynamics.

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 IRT.

9.4 Study Procedures

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable (up to 4 days) for inclement weather, holidays, vacations, and other administrative reasons or a longer window after discussion with the sponsor project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

Patients will be evaluated at scheduled visits over the following study periods: screening, treatment, EOT visit, and follow-up (PFS and OS), 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). The timing of the EOT visit should occur before any subsequent therapy is given or up to 30 days after the last dose of study drug, whichever occurs first.

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

9.4.1 Informed Consent

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

9.4.2 Patient Demographics

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

9.4.3 Medical History

During the screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it and the best response achieved by each one. For example, patients with MM this would include the initial diagnosis date, stage of MM using the Revised International Staging System (ISS) system [39] and Salmon-Durie staging. Confirm that the medical status does not include active chronic HBV, HCV, or HIV infection. In addition, the history should include a review of all current medications; concomitant medications will be recorded as specified in Section 9.4.8. Severe acute respiratory syndrome cornoavirus 2 (SARS-CoV2) positive testing, COVID-19 infection, and COVID vaccination as appropriate prior to ICF should be captured as part of medical history.

[redacted].

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the screening visit. Symptom-directed assessments will be conducted at the times specified in the SOE (see Appendix A) as per standard clinical practice. Any changes in the symptom-directed assessments that are judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.0.

9.4.5 Patient Height and Weight

Height will be measured during the screening visit only. Weight will be measured on as indicated in the SOE and any time appropriate based on symptom directed assessments (Appendix A).

9.4.6 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). Additional details on drug administration days can be found in Section 8.1.1 for TAK-981 and Section 8.2 for daratumumab and hyaluronidase-fihj. Any vital sign value that is judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.0.

9.4.7 Pregnancy Test

A serum or urine pregnancy test will be obtained for women of childbearing potential at screening and as specified in the SOE (Appendix A). 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.

9.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent through the EOT visit or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.7.6 for a list of medications and therapies that are prohibited during the study.

9.4.9 Adverse Events

Monitoring of AE, 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.

9.4.10 Enrollment

Eligibility criteria and confirmatory study assessments must be confirmed during the screening period, after a patient has signed the ICF, and before receiving study drug. 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.

9.4.11 12-Lead ECG

A 12-lead standard safety ECG will be performed as specified in the SOE (Appendix A). A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

9.4.12 Clinical Laboratory Evaluations

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

9.4.12.1 Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the SOE (Appendix A). These labs will be performed locally.

Table 9.a Clinical Chemistry, Hematology, and Coagulation Tests

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

ANC: absolute neutrophil count; EDC: electronic data capture.
[a] neutrophils captured as ANC in EDC.

Table 9.b Clinical Urinalysis Tests and Creatinine Clearance

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.

Creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed 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.

Other formulas, such as estimated glomerular filtration rate (eGFR) or Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR) may be used after discussion with Takeda clinician/ designee if that is the standard formula used in the institution/ clinical center.

Any changes in clinical laboratory parameters that are judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.0.

9.4.12.2 Immunosafety Markers

Blood samples for the analysis of autoimmune endocrinopathies as shown in Table 9.c will be obtained as specified in the SOE (Appendix A). They will be performed locally only. Any changes in immunosafety markers that are judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.0.

Table 9.c Immunosafety Determinations in Serum

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

9.4.12.3 Blood Type Assessment

As discussed in Section 8.11.7, it is recommended that baseline type and serological screening be established before starting study treatment. This information may be available historically depending on previous exposure to a mAb. Patients should keep these results in case future transfusions are needed. Blood transfusion centers should also be informed of this interference with serological testing as necessary.

9.4.13 Myeloma Disease Assessment

Patients with MM will be assessed for disease response according to the IMWG criteria [23,24]. All procedures and tests should be done as outlined in the SOE (Appendix A). After 24 cycles on treatment, the patient may be monitored according to standard clinical practice per the treating physician.

Table 9.d Myeloma Disease Assessments

Serum/Urine	Bone Marrow/Imaging
SPEP	Bone marrow biopsy and/or aspirate [a]
UPEP	[redacted]
Immunofixation (serum and urine)	Imaging (skeletal survey, CT, PET/CT, MRI)
Quantification immunoglobulin levels	
Serum FLC	
Interference testing	

CT: computed tomography, FLC: free light chains; BMA: bone marrow aspirate; MRI: magnetic resonance imaging; PET: positron emission tomography; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis

[a] Clinically indicated BMA drawn prior to consent is acceptable for the baseline assessment provided that it is collected within 8 weeks of screening if acceptable results are available for morphology and clinical staging (Note details in Section 9.4.13.4). BMA will be needed during screening however for research samples.

For more details See Sections 9.4.13

9.4.13.1 β2-Microglobulin and Albumin

A blood sample will be collected during screening for measurement of serum β2-microglobulin and albumin for determination of disease stage according to the ISS; these results will be analyzed locally and recorded on the eCRF.

9.4.13.2 M-Protein Assessment

In addition to M-protein component assessment at screening and during treatment, a prior result most recent to the screening sample will also be obtained and entered in the EDC system in order to understand the kinetics of the disease progression.

For M-protein component quantification, samples will be obtained from all patients for SPEP, 24-hour urine collection for UPEP, serum FLC, serum and urine immunofixation testing, and total immunoglobulin levels will be obtained.

Exception: If the patient has measurable M-protein restricted to the urine, M-protein component quantification can be determined by UPEP only. Patients measurable by SPEP only will have 24-hour urine collected at screening and EOT and to document PR, very good partial response (VGPR), complete response (CR), or PD.

9.4.13.2.1 Immunofixation and Immunoglobulin Levels

Immunofixation will also be done to confirm CR.

Blood samples for IgG, IgA, and IgM will be obtained at screening and throughout the study at the time points specified in the SOE (Appendix A). Quantitative IgD and IgE will be done at screening only; unless it has already been documented that the patient has another type of MM and does not have IgD or IgE MM. For the rare patient with documented IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as IgG and IgA.

M-protein labs will be performed locally.

Serum and 24-hour urine samples will be collected as per the SOE (Appendix A).

9.4.13.3 Interference Testing

IgG mAbs as being given in this study can interfere with assays used to monitor endogenous M-protein. The SPEP and serum immunofixation can be positive due to mAb. This interference can impact the determination of CR and of disease progression in some patients with IgG myeloma protein.

Therefore, in patients with persistent VGPR by IMWG criteria where mAb interference is suspected or whenever the SPEP values reach ≤0.2 g/dL for 2 consecutive disease evaluations, a CR should be suspected triggering the need for interference testing. Currently, if the interference test results come back **positive**, then the assay is considered positive for endogenous protein, and thus there is still disease present. If the interference test results come back **negative**, then the assay is considered negative for endogenous protein, and thus the remaining protein is likely the mAb. This is communicated back to the sites, and the sites can proceed to perform a confirmatory BMA evaluation for possible CR if not already performed earlier.

Details on interference testing for patients on mezagitamab can be found in the laboratory manual.

Interference testing for patients receiving daratumumab and hyaluronidase would be done per the product label.

9.4.13.4 Bone Marrow Biopsy and/or Aspirate

A BMA must be obtained at screening for [redacted] molecular evaluation at a central laboratory. [redacted] BMA and/or biopsy results (from bone marrow done within 8 weeks of screening) for evaluation of morphology and clinical staging must be available at screening. If this is not available then morphology and clinical staging should be done from the BMA/biopsy at screening. [redacted]

A BMA is required during screening for molecular analyses including, [redacted] baseline clonal determination to aid in MRD evaluations [redacted].

Patients achieving a VGPR or suspected of achieving a CR should have a BMA collected at any time to document CR as per IMWG criteria and for MRD (see Section 9.4.13.3 for information regarding interference testing; and Appendix I for IMWG criteria). For patients achieving a VGPR the sample would be collected at approximately the first VGPR assessment.

- Suspected CR is defined independently of the immunofixation result; BMA is to be performed when the M-protein measurement in SPEP (for heavy-chain patients) or UPEP (for light chain patients) becomes below detection limits or nonquantifiable.
- The BMA samples may be evaluated locally with the exception of a sample of BMA that must be sent to the central laboratory for MRD analyses. Details on MRD testing can be found in the laboratory manual. The BMA samples will be evaluated to determine CR status. Determination of the kappa/lambda ratio by immunohistochemistry or immunofluorescence must be performed to assess for stringent CR (sCR).

In addition, a BMA is strongly recommended to investigate suspected PD if applicable.

9.4.13.5 Radiographic Assessment of Myeloma

Imaging to evaluate lytic and extramedullary disease will be performed at a minimum at screening and at the EOT visit. The choice of imaging modality (eg, skeletal survey, CT, magnetic resonance imaging [MRI], positron emission tomography–computed tomography [PET-CT]), is at the discretion of the investigator (according to institutional practice); however, all treatment phase and follow-up scans should use the same imaging modality used at screening to facilitate consistent disease assessment. Imaging tests will be done at screening (within 8 weeks of the first dose of study drug). If soft-tissue extramedullary disease is documented, repeat imaging should be performed as required to document response or progression as per IMWG standard criteria (refer to Appendix A). Additional imaging assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions).

Imaging will be analyzed locally, and reports maintained with the patient record for retrieval during monitoring visits. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate disease improvement.

9.4.14 PK Measurements

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

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

9.4.15 Pharmacodynamic Measurements

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

The following pharmacodynamic measures may be tested:

- TAK-981-SUMO adduct formation and SUMO2/3 inhibition in blood.
- [redacted]

9.4.15.1 [redacted]

[redacted]

9.4.15.2 BMA Samples for Molecular Analyses

BMA samples will be collected at screening and at suspected response (Refer to Section 9.4.13.4). The BMA collected at screening will be used to identify the patient's MM clones at baseline. The presence and abundance of these specific tumor clone(s) will be evaluated in the BMA sample collected at approximately the initial documentation of VGPR and suspected CR to determine the presence or absence of residual disease. If the clone is not identifiable at screening, an historical BM sample (ie diagnosis) will be requested to determine the underlying myeloma clone. A portion of the BMA samples may also be used for other molecular characterizations of the BM.

MRD status will be collected at VGPR or suspected CR (note Section 9.4.13.4), and if negative will be collected 6 months and 12 months later. If positive, MRD status will be evaluated later at a clinically relevant timepoint. If now negative, MRD should be repeated to confirm sustained negativity, as noted above.

9.4.15.3 Blood Samples for Pharmacodynamics [redacted]

Blood samples will be collected to demonstrate TAK-981-SUMO adduct formation, SUMO pathway inhibition, [redacted]

9.4.15.4 [redacted]

[redacted]

9.4.16 Immunogenicity and Sparse PK Sample Collection

Blood samples for the assessment of ADAs will be collected at time points specified in the SOE. Samples must be collected before mezagitamab or daratumumab is administered on a dosing day, and optionally at unscheduled visits for a subject who experiences an AE considered by the investigator to be consistent with mezagitamab/ daratumumab hypersensitivity/IRRs. A sample will be assessed for negative ADA, transiently and persistently positive ADA, ADA high and low titer.

ADA sample aliquots will be banked for future further ADA characterizations, which will depend on the clinical AE and the regulatory request.

Blood samples for sparse PK will be collected at time points specified in the SOE (Appendix A). The samples will be used for sparse PK and to confirm that mezagitamab and daratumumab are within the limits of assay tolerance to ADA presence.

9.4.17 [redacted]

9.4.17.1 [redacted]

[redacted]

9.4.17.2 [redacted]

[redacted]

[redacted]

9.4.17.3 [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 9.6.

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they 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 (defined in Section 9.10).
- Start of a new systemic anti-cancer treatment.
- Transfer 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). Refer to Section 9.8 regarding the consequence of study withdrawal.

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.

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Pregnancy.
- Withdrawal by subject.
- AE that leads to TAK-981 discontinuation.
- Treatment completion.

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

- AE/ SAE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

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

In the case of study closure (whether completion of the study or early study termination by the sponsor), eligible patients may have continued access to TAK-981 and/or mezagitamab (according to treatment cohort) as described in Section 6.5.5.

Note that some patients may discontinue study therapy for reasons other than PD before completing the full treatment course; these patients will remain in the study for PFS follow-up assessments as outlined in the SOE (Appendix A) until PD occurs. Unless the patient withdraws consent to follow-up, PFS and/or OS follow-up assessments will continue to be conducted as outlined in the SOE (Appendix A) and Section 9.10. Public records may be consulted as permitted per local regulations.

9.8 Withdrawal of Patients From Study

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

- Lost to follow-up.
- Study terminated by sponsor.

- Withdrawal consent by subject.
- Completed study.
- Death.
- Other.
- The consequence of a patient withdrawing consent from further treatment and/or follow-up is that no new information will be collected from the withdrawn patient and added to the existing data or any database. It is important to be clear what the patient is withdrawing consent from: treatment, follow-up or both. However, every effort will be made to follow all patients for safety. Data collected during patient consent, however, must be included in the database.
- Patients who are withdrawn from treatment during Phase 1b Cycle 1 for reasons other than DLT will be replaced.

9.9 Study Compliance

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

9.10 Posttreatment Follow-up Assessments (PFS and OS)

Patients who discontinue study treatment for reasons other than disease progression will continue PFS follow-up every 4 (±1) weeks from the EOT until the occurrence of PD, death, the start of subsequent anticancer therapy, other discontinuation criterion is met, study termination, or until 50% of patients have PD, whichever occurs first. (Section 9.7). Patients in follow-up will continue with disease assessment as described in Section 9.4.13. 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 who stop treatment due to PD will be followed every 12 (±1) weeks after documented PD for OS until death, loss to follow-up, consent withdrawal, study termination, for up to 12 months after the last patient discontinues or completes treatment, or until 50% of patients have died, whichever occurs first. Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, Social Security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

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

See Appendix A for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during

posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

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

transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0 [26], except CRS which will be graded according to ASTCT Consensus Grading for CRS [27]. 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.

10.2 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 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 trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; eg, surgery was performed earlier or later than planned.

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

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, [26], except CRS, which will be graded according to ASTCT Consensus Grading for CRS [27]. The criteria are provided in the study manual.

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

10.3 Monitoring of AEs and Period of Observation

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

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

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

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

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

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

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as 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 trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 SMC

During the study, an SMC composed of the principal investigators, and sponsor clinician will regularly review safety data to ensure patients' safety throughout the study and make decisions on Phase 1b dose escalation and on Phase 2 expansion as defined for the SMC within this protocol.

In accordance with Takeda standard operating procedures and considering applicable regulations and guidance, each clinical trial is evaluated to determine if an Independent Data Monitoring

Committee (IDMC) should be convened. An IDMC is not indicated at this time for this study given Takeda's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, which are appropriate for the ongoing monitoring of patient safety and data integrity. However, taking into consideration the evolving benefit/risk profile of the combinations being evaluated, the decision to convene an IDMC could be taken any time during the conduct of Study TAK-981-1503.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all

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

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

The analysis sets will include the following:

Safety analysis set: Patients who have received at least 1 dose, even if incomplete, of any study drug will be used for all safety analyses and for some efficacy analyses.

PK analysis set: Patients with sufficient dosing and TAK-981 PK data to reliably estimate 1 or more TAK-981 PK parameters for PK analyses.

Immunogenicity Set: Patients who receive at least 1 dose of anti-CD38 monoclonal antibodies and have an ADA status assessment at baseline, and at least 1 post-baseline sample.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive at least 75% of planned TAK-981 doses, all mAb doses, and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the Phase 1b portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Response-evaluable analysis set:. The response-evaluable analysis set is a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 posttreatment

evaluation. The response-evaluable population will be used for the analyses of response rates, TTR, DOR, and PFS for patients in Phase 1b.

Modified intent-to-treat (mITT) analysis set: The mITT population is defined as all patients who receive at least 1 dose of any study drug in the Phase 2 part of the study, or who receive at least 1 dose of any study drug and are treated at the Phase 2 dose level in the Phase 1b part of the study. The mITT population may be used for the sensitivity analyses of efficacy endpoints.

Pharmacodynamic analysis sets:

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

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

[redacted]

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

Phase 1b:

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

In the Phase 1b portion of this study, efficacy parameters such as ORR and CBR 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 for each regimen based on investigator's assessment based on standard disease response criteria.

ORR is defined as the proportion of patients who achieve PR or better (determined by the investigator) during the study based on IMWG criteria.

The primary efficacy analysis will be based on the response-evaluable population.

Estimates of the ORR will be presented with 2-sided 95% exact binomial confidence intervals.

13.1.3.2 Secondary Efficacy Analysis

Phase 1b:

Secondary efficacy endpoints in Phase 1b portion include ORR and CBR.

ORR is defined as the proportion of patients who achieve PR or better (determined by the investigator) during the study based on IMWG criteria.

CBR for each regimen based on investigator's disease assessment (response of at least stable disease for at least 3 months or better) based on IMWG criteria.

These efficacy analyses will be based on the response-evaluable population.

Estimates of the ORR and CBR will be presented with 2-sided 95% exact binomial confidence intervals.

Phase 2:

Secondary efficacy endpoints in Phase 1b portion include DOR, time to response, TTP, TTNT, 1-year 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 PD for responders (PR or better). Responders without documentation of PD will be censored at the date of last response assessment that is stable disease or better.

Time to Response is the time from the date of the first dose to the date of the first documentation of objective response as defined by standard disease criteria.

TTNT is defined as the time from the date of first dose randomization to the date of the first dose initiation of the next line of antineoplastic therapy, for any reason. Patients who have not started the second-line therapy will be censored at date of last known to be alive subsequent anti-cancer therapy.

TTP is defined as the time from the date of the first dose to the date of the first documentation of PD as defined by standard disease criteria.

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

by IMWG criteria. Patients without documentation of PD will be censored at the date of the last response assessment.

OS is defined as the time from the date of randomization 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.

TTNT, TTP, PFS, and OS will be analyzed descriptively using Kaplan-Meier (KM) method for safety analysis set. DOR will be analyzed using KM method for response-evaluable analysis set. Time to response will be summarized descriptively for response-evaluable analysis set.

Selected efficacy endpoints may be analyzed using mITT population. Further details on the efficacy endpoint analyses will be discussed in the SAP.

13.1.4 PK Analysis

13.1.4.1 PK of TAK-981

The PK of TAK-981 will be characterized in this study.

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

- C_{max} (maximum observed plasma concentration).
- t_{max} (time of first occurrence of maximum observed concentration).
- AUC_{∞} (area under the plasma concentration-time curve from time 0 to infinity).
- AUC_t (area under the plasma/blood/serum concentration-time curve from time 0 to time t).
- $t_{1/2z}$ (terminal disposition phase half-life).
- Total clearance (CL).
- V_{ss}.

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

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

13.1.4.2 PK of Mezagitamab/ Daratumumab

Mezagitamab or daratumumab concentrations will be summarized using descriptive statistics. Individual mezagitamab or daratumumab concentration-time data will be presented in listings and tabulated using summary statistics by dose cohort.

13.1.5 Pharmacodynamic Analysis

The analysis of biomarker profiles for each dose and timepoint tested will be tabulated. When possible, the dynamic range for each biomarker and fold change will be determined to better understand TAK-981 biological activity range and duration of pharmacodynamic effect, and to help determine the PAD/RP2D for the TAK-981 in each antibody combination. In addition, candidate response biomarkers will be evaluated.

13.1.6 PK/Pharmacodynamic Analysis

13.1.6.1 PK/Pharmacodynamic Analysis

Data permitting, the PK and pharmacodynamic data collected in this study will be analyzed to understand the exposure-response relationship for TAK-981 in combination with anti-CD38 mAbs. Such analysis may be performed on an ongoing basis to assess the appropriateness of dose and schedule of TAK-981 in combination with mezagitamab or daratumumab and hyaluronidase-fihj and for determination of PAD.

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

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

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

In addition, the PK-pharmacodynamic data collected in the study during dose escalation may be used to inform the quantitative systems pharmacology model that may be used to further refine the dose/schedule for TAK-981. Furthermore, the PK-pharmacodynamic data collected in this

study may be pooled with similar data from other clinical studies for population analysis purposes. The results of such PK-pharmacodynamic and population PK-pharmacodynamic analyses and quantitative systems pharmacology modeling may not be presented in the CSR for this study but will be presented in a separate report.

13.1.6.2 MRD Analysis

MRD negativity is defined as the absence of MRD and MRD positivity is defined as the presence of MRD. For patients with suspected CR or VGPR, MRD assessment will be conducted on BMA collected at screening and at time of suspected CR and VGPR. The BMA collected at screening will be used to identify the patient's MM clones at baseline. The presence and abundance of these specific tumor clone(s) will be evaluated in the BMA sample collected in patients who achieve a VGPR or suspected CR to determine the presence or absence of residual disease.

The number and percentage of patients with MRD negative status as determined by NGS will be summarized.

In addition, MRD negative rate over time, defined as percentage of participants who have achieved MRD negative status at 1 year, will be also summarized.

Further details on the MRD analyses will be discussed in the SAP.

13.1.7 Immunogenicity Analysis

Immunogenicity will be summarized using the Immunogenicity set. Descriptive statistics will be used to summarize subjects in the following categories: ADA negative, transiently and persistently ADA positive, low or high ADA titer.

The relationship between immunogenicity status (ADA and ADA titer) and PK (mezagitamab and daratumumab) and safety may be explored. Further details will be provided in the SAP.

13.1.8 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set.

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

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

AEs will be tabulated according to the 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 Scores will be summarized using a shift table.

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

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

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

13.1.9 [redacted]

13.1.9.1 [redacted]

[redacted]

13.1.9.2 [redacted]

[redacted]

[redacted]

13.1.9.3 [redacted]

[redacted]

13.2 Interim Analysis and Criteria for Early Termination

Although no formal interim analysis is planned, investigators and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort in the dose escalation phase (see Section 8.5) and during Phase 2, as described in Section 6.3.1.

During the Phase 2 part of the study, if any arm shows an ORR below the futility boundary in the first stage, then the enrollment in that specific arm will be stopped (see Section 13.3).

13.3 Determination of Sample Size

The iBOIN design will be implemented for the dose escalation phase. It is estimated that up to approximately 30 DLT-evaluable patients will be enrolled to evaluate dose escalation for 2 dosing schedules of TAK-981 combining with mezagitamab, with up to approximately 15 patients for each dosing schedule.

After RP2D is defined, dose escalation of TAK-981 in the combinations of daratumumab and hyaluronidase-fihj will be evaluated using the similar iBOIN design. It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate dose escalation doses for this combinations.

Efficacy Evaluation (Phase 2):

[redacted]

[redacted]

Table 13.a [redacted]

[redacted]

Patients enrolled at the Phase 2 dose levels in the Phase 1b portion of this study will be included in the Phase 2 portion of this study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, 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[FDA], the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). 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 and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide 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 or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site 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 trial. Until the site receives drug/notification, no protocol activities, including screening, may occur.

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

approvals and relevant documentation for these items must be provided to the sponsor (or 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 be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor-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.govand 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.

16.0 REFERENCES

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Appendix A SOEs

Table A-1 SOEs (28-Day Cycle)

Study Procedures	Screening	Treatment Period [a]													EOT	Follow-up	
		28-Day Cycles														PFS	OS
Cycle		Cycles 1 and 2					Cycles 3 to 6				Cycle 7 and Beyond				Up to 30 Days After Last Dose	Every 4 Weeks Until PD	Every 12 Weeks After PD
Days	-28 to -1	1	2 [b]	8	15	22	1	8	15	22	1	8	15	22			
Window		±2 Days													+1 Week	±1 Week	±1 Week
Informed consent[c]	X																
Eligibility criteria[d]	X																
Demographics	X																
Complete medical history	X																
BMA for baseline morphology/ clinical staging	X[e]																
Complete physical exam	X														X		
Symptom-directed physical exam		X					X				X						
ECOG performance status	X	X					X				X				X		
Height	X																
Weight	X														X		
Vital signs[g]	X	X		X	X	X	X		X		X				X		
Blood type assessment	X																
12-lead ECG[h]	X	X[h]		X[h]	X[h]		X[h]				X[h]				-		
Safety Laboratory Assessments																	
Window	X	±2 Days													+1 Week	±1 Week	±1 Week
Pregnancy test[i]	X	X					X				X				X		
Hematology[j]	X	X		X	X	X	X		X		X				X		
Clinical chemistry[j]	X	X					X				X				X		

Coagulation[j]	X						X				X				X		
Direct/indirect coombs[j]	X	X					X				X				X		
Urinalysis[j]	X						X				X				X		
Immunosafety markers[k]	X	X					X								X		
Disease Assessment Tests																	
M-protein measurements (SPEP/UPEP)[l]	X	X			X		X				X				X	X	X
Albumin and β2-microglobulin	X																
Serum free light chain assay[l]	X	X			X		X				X				X	X	X
Immunofixation - serum and urine[l,m]	X	X			X		X				X					X	X
Quantification of immunoglobulins[n]	X	X					X				X					X	X
BMA (disease assessment)[f]		At suspected CR and VGPR to document CR/stringent CR [sCR]. See Section 9.4.13.4 for more detail													X optional at relapse		
[redacted]																	
BMA sample for MRD	X[e]	At suspected CR and VGPR. If negative, at 6 and 12 months later. Should be repeated if MRD positive at a clinically relevant timepoint. If now negative at subsequent testing, BMA should also be repeated to support sustained MRD status as noted above.															

Imaging Disease Assessment																
Bone imaging[p]	X	Additional assessments for bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD).														
Soft-tissue plasmacytoma[q]	X	If disease is documented at screening, repeat scanning performed as required to document a response or PD. Additional assessments for bone disease can be done per PI discretion														
Investigator's assessment of disease response/status		C2					X				X				X	X
Biologic Assessments																
Pharmacodynamic [redacted]		Refer to Table A-5 and Table A-6 for timepoints.														
Immunogenicity (serum)[r]		Refer to Table A-5 and Table A-6 for timepoints.														
PK		See details in Table A-4.														
Additional Assessments and Monitoring																
[redacted]																
Concomitant medications and procedures monitoring		Recorded from the signing of the ICF to 30 days after last dose of study therapy														
AE reporting[t]		Events of new onset are to be recorded from the signing of ICF to 30 days after last dose of study therapy (see Section 10.3)														
		SAEs are to be collected from the signing of the ICF to 30 days after last dose of study therapy (see Section 10.3)														
New primary malignancy[u]		Assessment continuous from the start of study drug until death or termination of the study by the sponsor														
Survival																X
Subsequent therapy																X[v]
Drug Administration																
Premedication		See details provided in Table A-2 and Table A-3.														
TAK-981		See details provided in Table A-2 and Table A-3.														
Monoclonal antibody		See details provided in Table A-2 and Table A-3.														

AE: adverse event; BMA: bone marrow aspirate; C: cycle; C1D1; Cycle 1, Day 1; COVID-19: coronavirus disease 2019; CR: complete response; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EORTC: European Organization for

Research and Treatment of Cancer; EOT: end-of-treatment; [redacted]; HBV: hepatitis B virus; HCV: hepatitis C virus; IAR: injection-associated reactions; ICF: informed consent form; Ig: immunoglobulin; IMWG: International Myeloma Working Group; IRR: infusion-related reaction; IV: intravenous; MM: multiple myeloma; MRD: minimal residual disease; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PO: oral; [redacted]; PR: partial response; [redacted]; QOL: quality of life; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; SOE: schedule of event; SPEP: serum protein electrophoresis; TEAE: treatment-emergent adverse event; UPEP: urine protein electrophoresis; VGPR: very good partial response.

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

[b] Day 2 visit is only applicable for Cycle 1.

[c] Informed consent must be documented before initiating any screening procedures that are for research purposes. Tests such as UPEP which are done for standard of care, may be done before consent.

[d] Screening period is 28 days (ie, Day -28 to Day -1). Confirmation of patient eligibility by a Takeda project clinician or designee is required before enrollment.

[e] A BMA prior to consent is acceptable for the baseline assessment of morphology and clinical staging provided that it is collected within 8 weeks of screening and the BMA was adequate. If this is not available a BMA at screening is required (refer to Section 9.4.14.3). [redacted]

[f] BMA will be done when the patient is in a VGPR or suspected CR to document CR/sCR. See Section 9.4.13.4 for definition of suspected CR. A portion of this BMA (second pull) at approximately the first occurrence of VGPR and suspected CR will also be used for MRD assessment (refer to Section 9.4.15.1).

[g] Vital signs (temperature, blood pressure, and heart rate) must be monitored before, during, at the end of administration of TAK-981, 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. During C1, vital signs need to be monitored as above and up to 4 hours after the end of the infusion (for C1D1). From C2 onwards, vital signs will be monitored immediately before the start of infusion and after the end of infusion, and the patient can be discharged from the site per investigator discretion. During daratumumab infusions, vital signs should be checked before the start of the infusion, at the end of the infusion, and as medically appropriate duringthe infusion based on patient symptomatology according to the respective prescribing information.

[h] Single safety ECGs will be collected at Phase 1b only screening, pre- and post-EOI (+1 h window) on C1D1, D8, D15 and C2D1, D8, D15, then predose C2 and beyond every other cycle (so C2D1, C4D1, C6D1 etc). Single safety ECGs will be collected at Phase 2 only screening, predose C1, C2 then every other cycle so (C2D1, C4D1, C6D1 etc). Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

[i] A serum or urine 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.

[j] Hematology, chemistry, coagulation laboratory samples and urinalysis will be collected locally and may be collected up to 3 days before Day 1 dosing and within 24 hours before subsequent dosing days, where required. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs). From Cycle 3 onwards, urine tests will be taken only the first day of each cycle and at end-of-treatment.

[k] 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.

[l] Clinical laboratory evaluations for disease assessments (SPEP, UPEP, serum free light chain, immunofixation, and immunoglobulin) must be tested locally. Sample requirements may vary depending on how the disease is measured. A 24-hour urine collection for UPEP is required only if urine M-protein is measurable at C1D1. If, at C1D1, urine M-protein is measurable by SPEP, UPEP may not be required at each visit. However, following IMWG criteria, all clinical laboratory parameters are required in all patients to document PR, VGPR, and CR at EOT, and to determine PD during PFS follow-up. For example, for patients measurable by SPEP, a 24-hour urine collection is required to document and confirm (as required by IMWG) PR, VGPR, CR, or PD. In addition to M-protein component assessment at screening and during treatment as per above, a prior result most recent to the screening sample will also be obtained in order to understand the kinetics of the disease progression.

[m] Immunofixation is to be done to confirm CR (undetectable M-protein by protein electrophoresis in both serum and urine will lead the central laboratory to perform immunofixation testing in both serum and urine). See Section 9.4.13.3 for details about interference testing and Section 9.4.13.4 for definition of suspected CR. "Suspected CR is defined independently of the immunofixation result; BMA is to be performed when the M-protein measurement in SPEP (for heavy-chain patients) or UPEP (for light chain patients) becomes below detection limits/nonquantifiable."

[n] Blood samples for IgG, IgA, and IgM will be obtained at screening and throughout the study at the time points specified; testing will be performed at a local laboratory. IgD and IgE are rare myeloma types; see Section 9.4.13.2. If a patient has documented IgD or IgE type myeloma subsequent samples will be evaluated as for IgG, IgA, and IgM as above.

[redacted].

[p] Imaging to assess status of bone disease will be done at screening (within 8 weeks before first dose of study drug) for all patients by means of skeletal survey, CT, MRI, or PET-CT. Additional assessments for bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) and should be done by the same modality. Imaging is considered standard of care and will be interpreted locally.

[q] Imaging to assess extramedullary disease will be done at screening (within 8 weeks of the first dose of study drug) for all patients by means of CT, MRI, or PET-CT. Additional imaging (x-ray, CT, or MRI) may be performed at the investigator's discretion (eg, in case of bone pain). If disease is documented at screening, then a repeat scan should be performed as required to document a response or PD. Follow-up scans should use the same imaging modality used at screening. Imaging is considered standard of care and will be interpreted locally.

[r] To be performed before administration of study dosing

[redacted]

[t] AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), until start of second-line alternative therapy, or 6 months after PD has occurred, whichever comes first.

[u] Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination. Assessments can be made over the phone and do not require a clinic visit. Data may be collected by methods that include but are not limited to telephone, e-mail, mail, and social security indexes.

[v] For subsequent therapy, type of therapy, start and end date, best response, and date of progression should be recorded in the eCRF if available.

Table A-2 Weekly Dosing Schedules

Window	**± 2 days**											
Weekly TAK-981 Dosing With Mezagitamab Regimen												
Cycle	28-day Cycles C1 and 2				28-day Cycles C3 through 6				28-day Cycles C7 through PD			
Day of cycle	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22
Premedication [a]	X	X	X	X	X		X		X			
TAK-981 [b]	X	X	X	X	X		X		X			
Mezagitamab [b, c]	X	X	X	X	X		X		X			
Weekly TAK-981 Dosing With Daratumumab and Hyaluronidase-fihj Regimen												
Premedication [a]	X	X	X	X	X		X		X			
TAK-981 [b]	X	X	X	X	X		X		X			
Daratumumab and hyaluronidase-fihj [b]	X	X	X	X	X		X		X			

C: cycle; C1D1, Cycle 1, Day 1; C1D8: Cycle 1, Day 8; D: day; PD: progressive disease.

[a] Premedication of dexamethasone, oral antipyretics and oral antihistamine will be administered. See Section 8.1.2 and Section 8.2.1 for more premedication/ postmedication details.

[b] For C1D1 only, the monoclonal antibody will be administered first (before the TAK-981 infusion). Starting at C1D8 onwards, TAK-981 will be administered before the monoclonal antibody. See Section 8.1. for more details about the order of drug administration.

[c] For mezagitamab: time and anatomical site should be recorded for each injection.

Table A-3 BIW Dosing Schedules

Window	**± 2 days**														
BIW TAK-981 Dosing With Monoclonal Antibody															
Cycle	28-day Cycles C1 and C2							28-day Cycles C3 through 6				28-day Cycles C7 through PD			
Day of cycle	D1	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22	D1	D8	D15	D22
Premedication [a]	X		X		X		X	X		X		X			
TAK-981 [b]	X	X	X	X	X			X		X		X			
Monoclonal antibody [b, c]	• Mezagitamab D1, 8, 15, 22 Cycle 1 and 2, then Day 1 and 15 Cycles 3 through 6, followed by once every 4 weeks Cycle 7 through PD • Daratumumab and hyaluronidase-fihj D1, 8, 15, 22 Cycle 1 and 2, then Day 1 and 15 Cycles 3 through 6, followed by once every 4 weeks Cycle 7 through PD														

C: cycle; C1D1: Cycle 1 Day 1; C1D8: Cycle 1, Day 8; D: day; PD: progressive disease.

[a] Premedication of dexamethasone, oral antipyretics and oral antihistamine will be administered. See Section 8.1.2 and Section 8.2.1 for more premedication/ postmedication details.

[b] For C1D1 only, the monoclonal antibody will be administered first (before the TAK-981 infusion). Starting at C1D8 onwards, TAK-981 will be administered before the monoclonal antibody. See Section 8.1. for more details about the order of drug administration.

[c] For mezagitamab: time and anatomical site should be recorded for each injection.

Table A-4 TAK-981 Plasma PK Sampling: Phase 1b and Phase 2

	Cycle 1			Cycle 2	
	Day 1	Day 8	Day 15	Day 1	Day 15
	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)	PK (Plasma)
Phase 1b					
Pre-TAK-981 dose (within 1h before the start of infusion)	X	X	X	X	X
End of TAK-981 infusion (±10 min)	X	X	X	X	X
2 h after end of TAK-981 infusion (±30 min)	X				
4 h after end of TAK-981 infusion (±30 min)	X				
24 h after end of TAK-981 infusion (±60 min)	X				
Total time points/samples	5	2	2	2	2
Phase 2					
Pre-TAK-981 dose (within 1 h before the start of infusion)	X		X	X	X
End of TAK-981 infusion (±10 min)	X		X	X	X
1-4 h after end of TAK-981 infusion (±30 min)	X				
Total time points/samples	3	0	2	2	2

h: hour; PK: pharmacokinetic(s).

Table A-5 Clinical Sample Collection: Phase 1b

	Screening	C1D1				C1D8		C1D15	C2D1	C2D15	C3D1, C6D1, C9D1, C12D1	Suspected CR and Initial VGPR	6 and 12 Months after Confirmed Negative MRD	EOT
		Predose	1 h post-EOI (±20 min)	4 h post-EOI (±60 min)[a]	24 h post-EOI (±60 min)	Predose	1 h post-EOI (±20 min)	Predose	Predose	Predose	Predose			
BMA for [redacted] r MRD	X[b]											X	X	
Serum sample for immunogenicity (ADA/titer)[c]		X							X		X			X
Serum sample for sparse mezagitamab/daratumumab PK		X							X		X			X
Serum sample for mezagitamab or daratumumab interference[d]								See Section 9.4.13.3.						
[redacted]														
Whole blood sample adducts/conjugates[e]		X	X	X	X	X	X	X	X	X	X			X
[redacted]														

ADA: antidrug antibodies; AE: adverse event; BMA: bone marrow aspirate; C: cycle; C1D1: Cycle 1, Day 1; D: day; CR: complete response; EOT: end of treatment; MRD: minimal residual disease; SC: subcutaneous; VGPR: very good partial response.

[a] If daratumumab and hyaluronidase-fihj is administrated SC on C1D1: do not collect the 4 hours postdose biomarker samples.

[redacted]

[c] Serum samples for immunogenicity will be collected at baseline (before mezagitamab or daratumumab administration on Day 1) and immediately prior to dosing at each indicated visit. Collection will also take place when a patient experiences a treatment-emergent AE consistent with hypersensitivity/infusion-related reaction.

[d] Daratumumab interference analysis to be performed at local laboratory, per label.

[redacted]

Table A-6 Clinical Sample Collection: Phase 2

	Screening	C1D1	C2D1	C3D1, C6D1, C9D1, C12D1	Suspected CR and Initial VGPR	6 and 12 Months after Confirmed Negative MRD	EOT
		Predose	Predose	Predose			
BMA for [redacted] MRD	X[d]				X	X	
Serum sample for immunogenicity (ADA/titer)[a]		X	X	X			X
Serum sample for sparse mezagitamab/daratumumab PK		X	X	X			X
Serum sample for mezagitamab interference[b]			See Section 9.4.13.3.				
[redacted]							

ADA: antidrug antibodies; AE: adverse event; BMA: bone marrow aspirate; C: cycle; C1C1: Cycle 1, Day 1; D: day; CR: complete response; EOT: end of treatment; IR: infusion reaction; MRD: minimal residual disease; VGPR: very good partial response.

[a] Serum samples for immunogenicity will be collected at baseline (before mezagitamab administration on Day 1) and immediately prior to dosing at each indicated visit. Collection will also take place when a patient experiences a treatment-emergent AE consistent with hypersensitivity/IR.

[b] Daratumumab interference analysis to be performed at local laboratory, per label.

[redacted]

Appendix B Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 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 UK, 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 MM, 1982 [43].
ECOG: Eastern Cooperative Oncology Group.

Appendix E Methods of Contraception Considered to be Effective

A. Acceptable Methods Considered Highly Effective

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [a]:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation [a]:
  - Oral.
  - Injectable.
  - Implantable [b].
- Intrauterine device (IUD) [b].
- Intrauterine hormone-releasing system (IUS) [b].
- Bilateral tubal occlusion [b].
- Vasectomised partner [b, c].
- Sexual abstinence [d].

B. Methods That Are Considered Less Highly Effective

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

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

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

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

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

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

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

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

Appendix F Drugs that Interact With the CYP3A Family of Cytochromes P450

Drugs listed below 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 clarithromycin cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice idelalisib indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir nefazodone paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir and ritonavir telaprevir telithromycin tipranavir and ritonavir troleandomycin voriconazole
Moderate CYP3A Inducers [a]	**Moderate CYP3A Inhibitors** [b]
bosentan efavirenz etravirine phenobarbital primidone	aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil

CYP: cytochrome P450.

[a] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (accessed 05 August 2021).

[b] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (accessed 05 August 2021).

Appendix G Examples of Clinical Inhibitors of Pgp

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

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

Source: fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2 (accessed 05 August 2021).

Pgp: P-glycoprotein.

Appendix H iBOIN Design

In Phase 1b Part 1, It is estimated that up to approximately 15 DLT-evaluable patients will be enrolled to evaluate dose escalation for 1 dosing schedule of TAK-981 with 3 dose levels.

Dose escalation will follow an iBOIN design{Lee, 2019 #14382}. Each schedule will be evaluated separately. Approximately 3 patients will be enrolled in the first cohort. The decision to escalate or de-escalate the dose of TAK-981 will be based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the iBOIN model. The target DLT rate for this study is 0.3. According to the single agent Study TAK-981-1002, the prior DLT rate for the 3 doses are (0.25, 0.26, 0.5) and the prior effective sample size are (2, 2, 0). The total number of patients at each dose level could be up to approximately 9. The dose escalation and de-escalation rules for TAK-981 are as follows.

1. If the observed DLT rate at the current dose is $< \lambda_e$, escalate the dose to the next higher dose level;
2. If the observed DLT rate at the current dose is $> \lambda_d$, de-escalate the dose to the next lower dose level;
3. Otherwise, stay at the current dose.

The values for λ_e and λ_d vary with dose level and the number of patients treated on a dose. **Table H-1** provides an equivalent decision boundaries, which will be used in the trial for dose escalation and de-escalation.

Table H-1 Dose Escalation/De-escalation Rule for the iBOIN Design

	1	2	3	4	5	6	7	8	9
Dose level 1									
Escalate if # of DLT ≤	0	0	0	1	1	1	1	1	2
Deescalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥[a]	NA	NA	3	3	4	4	5	5	5
Dose level 2									
Escalate if # of DLT ≤	0	0	0	1	1	1	1	1	2
Deescalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5
Dose level 3									
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2
Deescalate if # of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5

DLT: dose-limiting toxicity; iBOIN: Bayesian Optimal Internal Design With Informative Prior; NA: not applicable.
[a] Eliminate the current and higher doses from the trial to prevent treating any future patients at these doses when they are overly toxic.

The operating characteristics of the iBOIN design based on 1000 simulations of each scenario are presented in the following table:

Table H-2 Operating Characteristics of the iBOIN Design

	1	2	3	Number of Patients	% Early Stopping
Scenario 1					
True DLT Rate	0.3	0.5	0.67		
Selection %	65.8	19.2	1		14
% Patients Treated	67	30.1	2.9	11.8	
Scenario 2					
True DLT Rate	0.13	0.3	0.48		
Selection %	23.5	55.5	20.5		0.5
% Patients Treated	39.7	42.3	18	14.3	
Scenario 3					
True DLT Rate	0.05	0.13	0.3		
Selection %	1.6	27.8	70.6		0
% Patients Treated	24.9	34.3	40.8	14.9	
Scenario 4					
True DLT Rate	0.05	0.1	0.2		
Selection %	1.7	12.8	85.5		0
% Patients Treated	24.2	29.7	46.1	14.9	

DLT: dose-limiting toxicity; iBOIN: Bayesian Optimal Internal Design with Informative Prior.
"% Early Stopping" refers to early stopping due to excessive DLT.

The operating characteristics show that the proposed iBOIN design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3. For example, in scenario 1, the first dose is the true MTD, and the iBOIN design yields the high selection percentage of 65.8% with 7.9 patients allocated to this dose level.

Appendix I Examples of QTc Interval Prolonging Agents (During Phase 1b 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 Risk of Torsade de Pointes, 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 J IMWG criteria

Response	Criteria
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h
	If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria
	If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30%
	In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required
	Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%
	In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
	No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following:
	Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or;
	Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or;
	Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
	Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%)
	Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder
	Two consecutive assessments before new therapy are needed

NOTE. Data adapted.[8,9,30a]
Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

IMWG = International Myeloma Working Group

Source: Rajkumar et al, 2011 [23], Palumbo et al 2014 [24]

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of new therapy. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL. Bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

Appendix K [redacted]

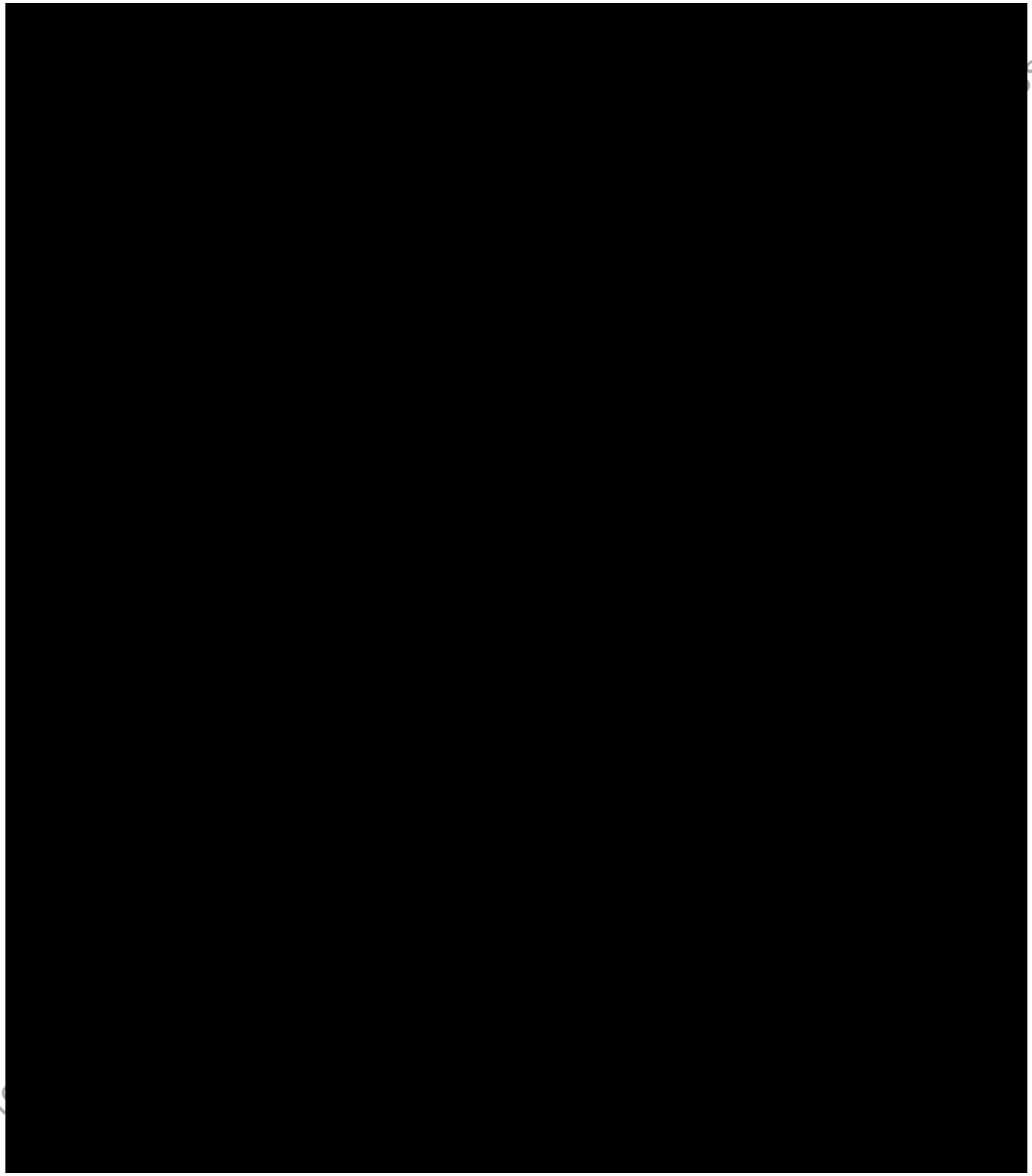
[redacted]

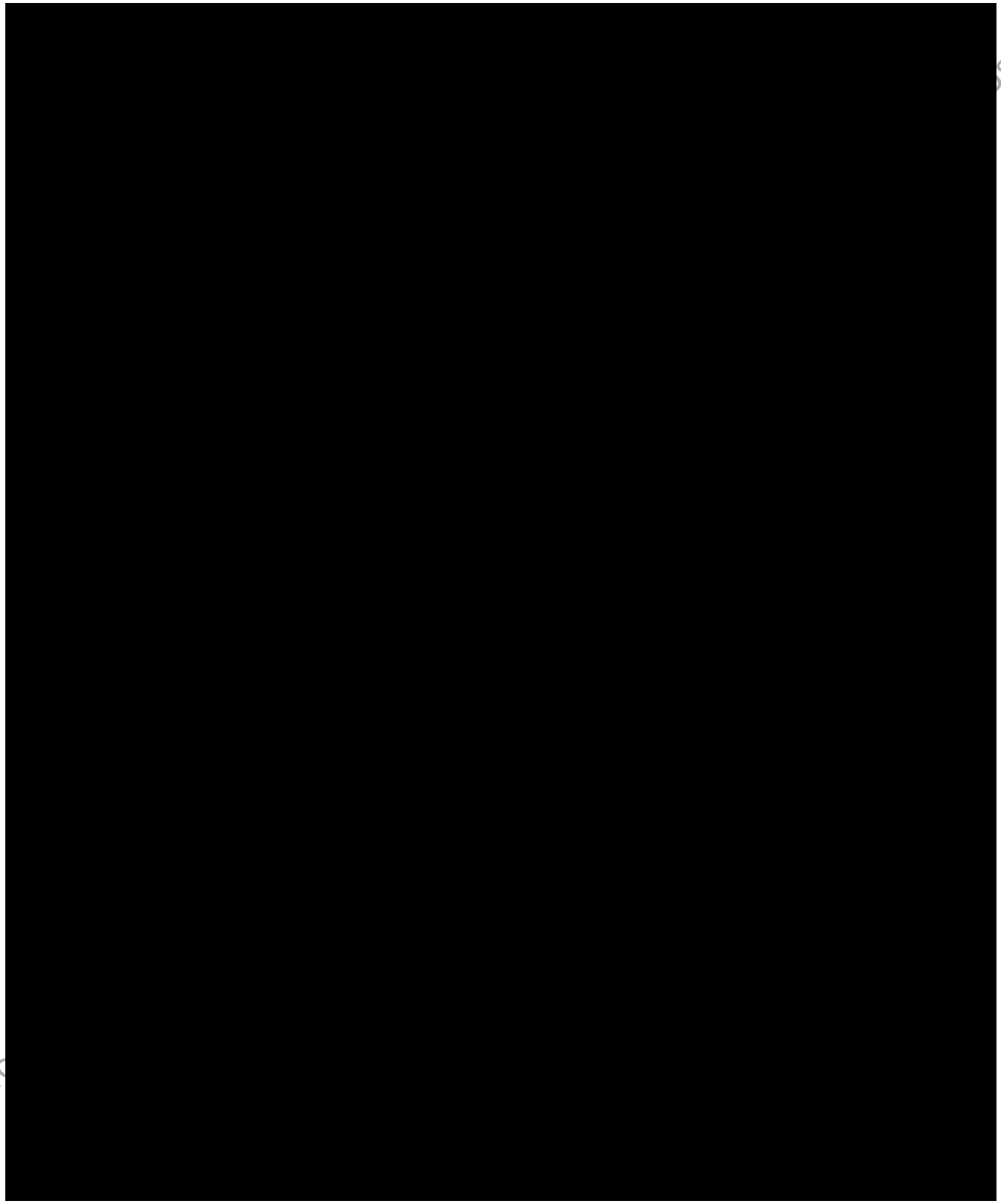
[redacted]

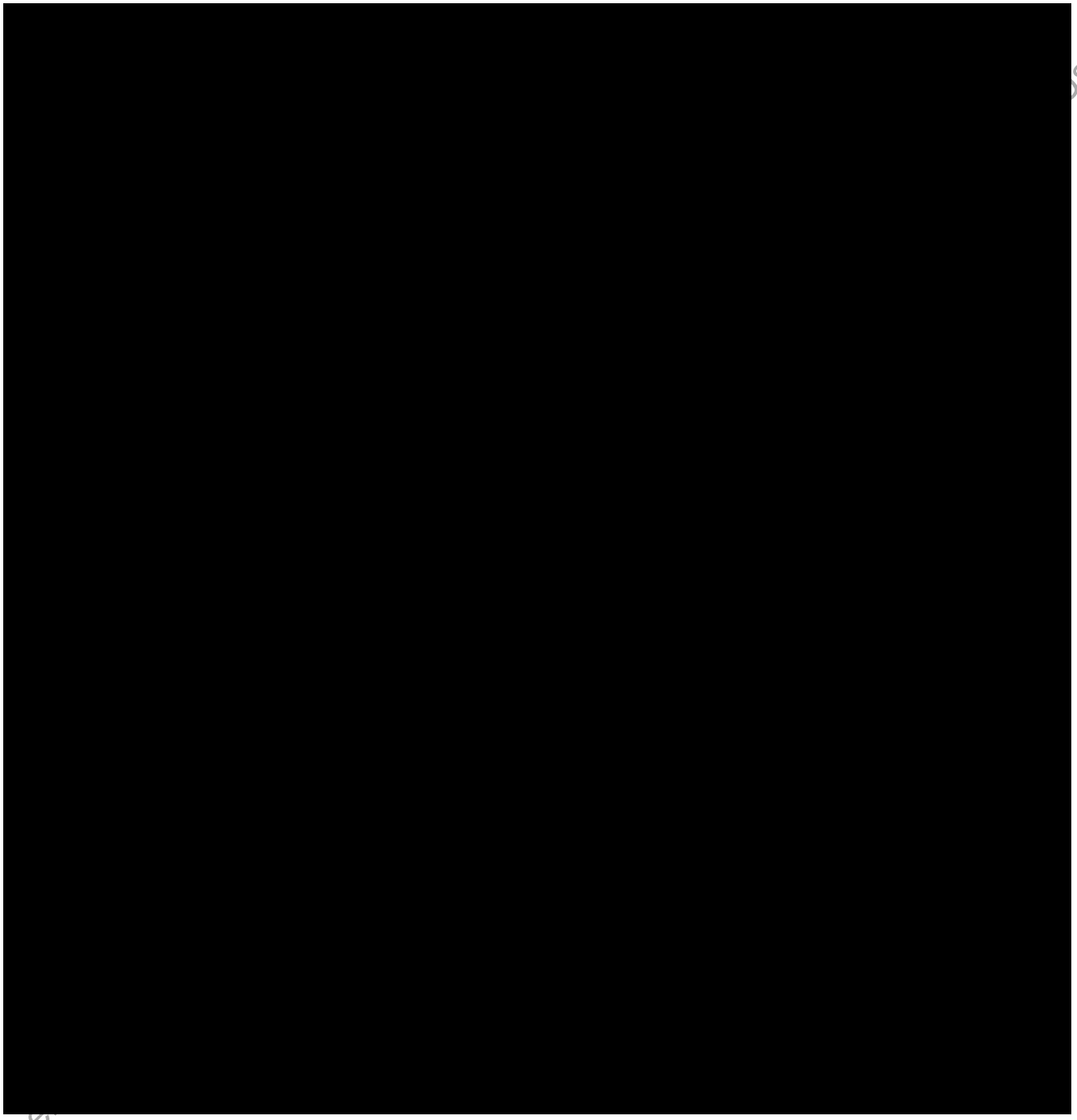
[redacted]

[redacted]

[redacted]







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Appendix L [redacted]

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Appendix M [redacted]

[redacted]

[redacted]

[redacted]

Appendix N Protocol History

Date	Amendment Number	Region
30 August 2021	Amendment 2	Global
22 December 2020	Amendment 1	Global
03 November 2020	Initial protocol	Global

Rationale for Amendment 1

This section describes the changes to the protocol incorporating Amendment 1.

The primary reason for this amendment was to address the changes requested by United States (US) Food and Drug Administration (FDA) during Investigational New Drug (IND) application review.

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

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 6.3 Phase 2 Study Design Section 13.2 Interim Analysis and Criteria for Early Termination	Added subsection for early stopping rules.	Changes made in response to FDA's request for addition of study stopping rules.
Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Modified inclusion criterion 3 to remove population of 2 or more lines of prior therapy.	Changes made in response to FDA's request to amend the inclusion criteria to limit the patient population to patients who have been treated with 3 or more lines of therapy.
Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Modified exclusion criterion 2 to clarify that patients participating in investigational vaccines or investigational medical device "for disease under study" will be excluded.	Change made for providing clarity on exclusion criterion.
Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria Section 8.8.1 Excluded Concomitant Medications and Procedures for TAK-981 Appendix I Examples of QTc Interval Prolonging Agents (During Phase 1 only)	Addition of exclusion criterion to exclude patients who require the use of drugs known to prolong the corrected QT (QTc) interval (during Phase 1 only). Addition of new appendix listing drugs known to prolong QTc interval.	Changes made in response to FDA's request to restrict concomitant use of drugs known to prolong the QT/QTc interval.

Protocol Amendment 1		
Summary of Changes Since Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.3 Definitions of DLT	Modified list of events that may be considered dose-limiting toxicities (DLTs).	Changes made in response to FDA's request for modifications of DLT definition.
Section 8.1.1 TAK-981 Study Drug Administration Section 8.2.1.1 Vital Signs	Incorporated additional vital sign monitoring.	Changes made in response to FDA's request.
Section 2.0 STUDY SUMMARY Section 8.5 Dose Escalation Rules	Provided more clarity on TAK-981 dose escalation with respect to recommended Phase 2 dose.	Changes made in response to FDA's request.
Section 8.9 Permitted Concomitant Medications and Procedures	Added language to discuss with sponsor/designee prior to initiation of a CoV2 vaccination and/or COVID-19 treatment.	Addition of language made to have more clarity on process to follow for initiation of a CoV2 vaccination and/or COVID-19 treatment.
Section 9.4.14.1 Primary Specimen Collection (Table 9.e) Section 9.4.17 Immunogenicity and Sparse PK Sample Collection Appendix A Schedule of Events, Table 5	Added collection of blood samples for sparse pharmacokinetics (PK).	Changes made in response to FDA's request to collect sparse PK samples to characterize the PK of mezagitamab in the proposed combination regimen.
Appendix A Schedule of Events, Table 1	Addition of 12-lead electrocardiograms (ECGs) to monitor QT interval, at pre-TAK-981 dosing, and end of TAK-981 infusion on Days 1 and 8 of Cycles 1 and 2 during Phase 1b.	Changes made in response to FDA's request to monitor ECGs at the expected maximum plasma concentration of TAK-981.
Section 8.10 Precautions and Restrictions	Clarified that if the last dose received is mezagitamab, contraception is required through 6 months.	Addition made to provide more clarity on contraception duration.
Appendix H iBOIN Design	Modified the appendix for clarity.	Modification made in response to FDA's feedback.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	31-Aug-2021 23:23 UTC
[redacted]	Clinical Approval	01-Sep-2021 14:23 UTC
[redacted]	Clinical Pharmacology Approval	01-Sep-2021 18:46 UTC
[redacted]	Clinical Approval	01-Sep-2021 23:30 UTC