CLINICAL STUDY PROTOCOL

NCT Number: NCT03439280

Study Title: A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

Study Number: TAK-079-1501

Protocol Versions and Date:

Version 3.0: 02 April 2019
Version 2.0: 18 May 2018
Version 1.0: 08 December 2017
Original Protocol: 12 October 2017

PROTOCOL

A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Study Number:	TAK-079-1501
IND Number:	136,414 **EudraCT Number:** Not applicable
Compound:	TAK-079
Date:	12 October 2017

[redacted]

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.0 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	See Section 10.0

[redacted]

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 on Harmonisation E6 Good Clinical Practice: 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]
Digitally signed by [redacted]
DN: cn=[redacted], o=unito, ou=unito, email=[redacted], c=IT
Date: 2017.10.13 15:09:10 +02'00'

Date

[redacted], MD, PhD
Global Medical Affairs
Distinguished Research Fellow Oncology

Date

[redacted], PhD
Global Statistics

Date

[redacted], PharmD, PhD
Quantitative Clinical Pharmacology

[redacted]

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

[redacted]

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-079	
Title of Protocol: A Phase 1/2a, Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma		
Study Number: TAK-079-1501	**Phase:** 1/2a	

Study Design:

This is a multicenter, open-label, dose-escalation, single-arm, phase 1/2a study designed to determine the safety and tolerability of TAK-079 monotherapy in patients with relapsed or refractory (r/r) multiple myeloma (MM), and to provide a preliminary assessment of its activity against r/r MM.

Once enrolled into the study, patients will receive TAK-079 via subcutaneous (SC) administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until disease progression (PD). Patients will receive ongoing treatment with TAK-079 until PD, unacceptable toxicities, or withdrawal due to other reasons.

The phase 1 portion of the study will evaluate administration of TAK-079 for dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) for further assessment in phase 2a. A recommended dose below the MTD may be identified based on the review of safety, pharmacokinetic (PK), [redacted], and clinical data from the phase 1 portion of the study.

The safety and tolerability of TAK-079 will be assessed by recording and analyzing treatment-emergent adverse events (TEAEs), dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology, urinalysis, electrocardiograms, and concomitant medications. In phase 1, approximately 5 doses of TAK 079 will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D.

It is expected that approximately 39 patients will be enrolled in the study. The estimated duration of the study is approximately 48 months (ie, 4 years).

Primary Objectives:

Phase 1

To determine the safety, tolerability, and the MTD/RP2D of TAK-079 monotherapy in patients with r/r MM.

Phase 2a

To provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with r/r MM.

Secondary Objectives:

Phase 1

- To investigate a potential MTD/RP2D of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

Phase 2a

- To further evaluate safety at the MTD/ RP2D.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

[redacted]

Exploratory Objectives:
Phase 1 and 2a

[redacted]

Subject Population: Subjects aged 18 years or older, with r/r MM, and Eastern Cooperative Group (ECOG) performance status of ≤2

Number of Subjects:	**Number of Sites:**
Phase 1: approximately 21 patients. Phase 2a: approximately 18 patients.	Phase 1: approximately 4 investigational centers. Phase 2a: approximately 6 investigational centers.
Dose Level(s): TAK-079 injections will be escalated as follows: 45 mg, 135 mg, 400 mg, 1200 mg, and 1800 mg in phase 1. After patients have received premedication treatment, doses will be administered with syringes as SC injections up to a maximum of 200 mg TAK-079 in 2 mL per injection, injected every 30 minutes until the full scheduled dose has been administered. Each dose will be administered as once weekly for 8 weeks (8 doses), then once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks until PD or unacceptable toxicities occur. For phase 2a, in the absence of DLT, the dose will be selected based upon review of the available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study. Premedication will be mandatory in phase 1. The decision to premedicate in phase 2a will be determined based on data from phase 1.	**Route of Administration:** Route of administration will be SC.
Duration of Treatment: TAK-079 will be administered until the patient experiences PD, unacceptable toxicities, or withdrawal due to other reasons.	**Period of Evaluation:** 21 days screening, ongoing treatment to PD. Patients who discontinue treatment for reasons other than PD will continue to be followed for progression-free survival (PFS) every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after the last patient has received their last dose (LPLD). Overall survival (OS): Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

[redacted]

Main Criteria for Inclusion:

Male and female patients, aged ≥18 years, with ECOG performance status of ≤2, requiring additional therapy as determined by the investigator. Patients must have received the final dose of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079: 120 days for antibody therapy (including anti-CD38), 90 days for autologous transplantation, and 30 days for chemotherapy, corticosteroid therapy (up to systemic equivalent of 10 mg daily prednisone allowed), radiation therapy, and major surgery. Patients must have adequate organ function as determined by the following laboratory values: absolute neutrophil count $\geq 1.0\times10^9$/L; platelets ≥75,000/mm^3 ($\geq 75\times10^9$/L); hemoglobin ≥7.5 g/dL; creatinine clearance ≥30 mL/min (Cockcroft-Gault); total bilirubin ≤1.5 times the upper limit of the normal range (ULN); and alanine aminotransferase/aspartate aminotransferase ≤2.5×ULN. Patients must have documented r/r MM per the International Myeloma Working Group (IMWG) criteria, with measurable disease defined as one of the following: serum M-protein ≥500 mg/dL (≥0.5 g/L) and urine M-protein ≥200 mg/24 hours. Patients without measurable M-protein in serum protein electrophoresis or urine protein electrophoresis must have a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal. Patients must have evidence of r/r MM as defined by the IMWG criteria, previously received at least 2 lines of myeloma therapy (including both an immunomodulatory agent and a proteasome inhibitor), and either be refractory or intolerant to at least one of these regimens. Prior treatment with an anti-CD38 monoclonal antibody (mAb) is allowed; however, CD38 expression must be significantly expressed on target cells for this mechanism of action to be effective. In the phase 2a portion of the study, patients must have been refractory to an anti-CD38 mAb therapy at any time during treatment.

Main Criteria for Exclusion:

Sensory or motor neuropathy of Grade ≥3, based on the National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) or not recovered from adverse reactions to prior myeloma treatments/procedures to NCI CTCAE Grade ≤1 or baseline; allogeneic stem cell transplant; congestive heart failure (New York Heart Association) Grade ≥II, cardiac myopathy, active ischemia, clinically significant arrhythmia, history of acute myocardial infarction within 5 months before enrollment, clinically significant uncontrolled hypertension, or any other uncontrolled cardiac condition or concurrent illness that would preclude study conduct and assessment; QT interval corrected by the Fridericia method >480 msec (Grade ≥2); history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-079 formulation (including patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction); history of myelodysplastic syndrome or another malignancy other than MM; clinical signs of central nervous system involvement of MM; or active chronic hepatitis B or C infection, active HIV infection, or active cytomegalovirus infection. Also excluded are patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance; smoldering myeloma; solitary plasmacytoma; amyloidosis; Waldenström macroglobulinemia or immunoglobulin M myeloma.

Endpoints (in order of importance):

Primary:

Phase 1

- The number of patients with TEAEs overall and per dose level.
  - Patients with DLTs at each dose level.
  - Patients with Grade ≥3 TEAEs.
  - Patients with SAEs.
  - Patients who discontinue because of TEAEs.
  - Patients with dose modifications (delays, interruptions, dose reductions).
    - Clinically significant laboratory values as determined by the investigator.
    - Clinically significant vital sign measurements as determined by the investigator.

Phase 2a

- Overall response rate (ORR), defined as the proportion of patients who achieved a partial response ([PR]; 50% tumor reduction) or better during study as defined by IMWG Uniform Response Criteria.

- **Secondary:**

[redacted]

- Phase 1
- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079 will be assessed in patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria.
  - Proportion of patients who achieved minimal response (MR), defined as 25% tumor reduction.
- Anti-TAK-079 antibody incidence and characteristics.
- Phase 2a
- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti-TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction, will be evaluated.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the time from the date of the first dose to the date of death due to any cause.
- Time to response, defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).
- **Exploratory:**

[redacted]

Statistical Considerations:

The MTD/RP2D will be estimated by an adaptive Bayesian Logistic Regression Modeling (BLRM) method with overdose control using data collected in the dose-escalation phase of the study. After review of the available safety, efficacy, PK [redacted] data, additional cohorts may be expanded by enrolling additional patients to obtain a more comprehensive assessment of disease response and to further inform selection of the R2PD.

Adverse events (AEs) will be summarized by treatment group and overall. Categorical variables such as ORR will be tabulated by treatment group and overall. Time to event variables such as DOR and PFS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided.

PK parameters will be summarized as appropriate.

Sample Size Justification:

Phase 1 of the study will follow an adaptive BLRM that implements escalation with overdose control. The 2-parameter model will be used and updated after each group of 3 patients is enrolled in the current dose level cohort.

[redacted]

For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

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

The selection of the next recommended dose will be determined from BLRM, along with consideration of other safety, clinical, PK, [redacted] data. Dose-escalation cohorts may be expanded to include additional patients to obtain a more comprehensive assessment of disease response before the phase 2a portion of this study is opened to enrollment. Approximately 5 dose levels are planned. For phase 1, the number of patients is planned to be approximately 21.

In phase 2a, approximately 18 additional patients will be treated to provide a preliminary estimate of the ORR in patients with r/r MM. All patients with MM must show clear evidence of PD with anti-CD38 therapy.

Phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

No prospective calculations of statistical power have been made; however, the following table shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this r/r population.

[redacted]

[redacted]

3.0 STUDY REFERENCE INFORMATION

Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (Appendix C). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

Principal Investigator

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

3.1 List of Abbreviations

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BLRM	Bayesian Logistic Regression Modeling
BMA	bone marrow aspirate
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form (refers to any media used to collect study data [ie, paper or electronic])
EOI	end of infusion
EOT	end of treatment
FDA	United States Food and Drug Administration
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin

Abbreviation	Term
[redacted]	[redacted]
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IR	injection reaction
IRB	institutional review board
IV	intravenous(ly)
LPLD	last patient, last dose
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAB	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PB	plasmablast
PD	progressive disease; disease progression
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS syndrome	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
PR	partial response
QTc	QT interval corrected for heart rate
RBC	red blood cell(s)
r/r	relapsed or refractory
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SCRS	severe cytokine release syndrome

Abbreviation	Term
SOE	Schedule of Events
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration
[redacted]	[redacted]
TTR	time to response
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WOCBP	women of child-bearing potential

4.0 INTRODUCTION

4.1 Background

TAK-079 is a fully human antibody of the immunoglobulin G1 (IgG1) subclass, which targets CD38 expressing cells for destruction through multiple mechanisms of action (complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity). TAK-079 treatment results in a rapid depletion of CD38+ leukocytes in the peripheral blood, as observed in nonhuman primate studies and in humans. A number of hematologic tumors express CD38, including multiple myeloma (MM), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and B-cell Non-Hodgkin's-lymphoma.

MM is a plasma cell-derived malignancy that accounts for approximately 1% of all cancers [1]. It is characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency. The 5-year survival rate of patients with MM is approximately 45% [1]. MM persists as a mostly incurable disease due to its highly complex and diverse cytogenetic and molecular abnormalities [2]. There has been improvement in the outcome for patients with MM in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory drugs (IMiDs) like lenalidomide, but patients who become refractory or are ineligible to receive PIs and IMiDs have a dismal prognosis [3]. In November 2015, the United States Food and Drug Administration (FDA) approved the CD38 antibody daratumumab (DARZALEX; Janssen) for the treatment of MM [4]. Daratumumab was studied in patients who had received at least 3 prior lines of therapy including a PI and an IMiD, or who were double-refractory to these agents. An overall response rate (ORR) of 29% was documented, including a 3% rate of complete response (CR)/stringent complete response (sCR). The main toxicity associated with daratumumab was infusion reactions, which were severe in some patients. Other common adverse reactions were fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection [5]. Notably, not all patients respond and many patients eventually develop progressive disease on daratumumab monotherapy [6].

4.2 Findings From Nonclinical and Clinical Studies

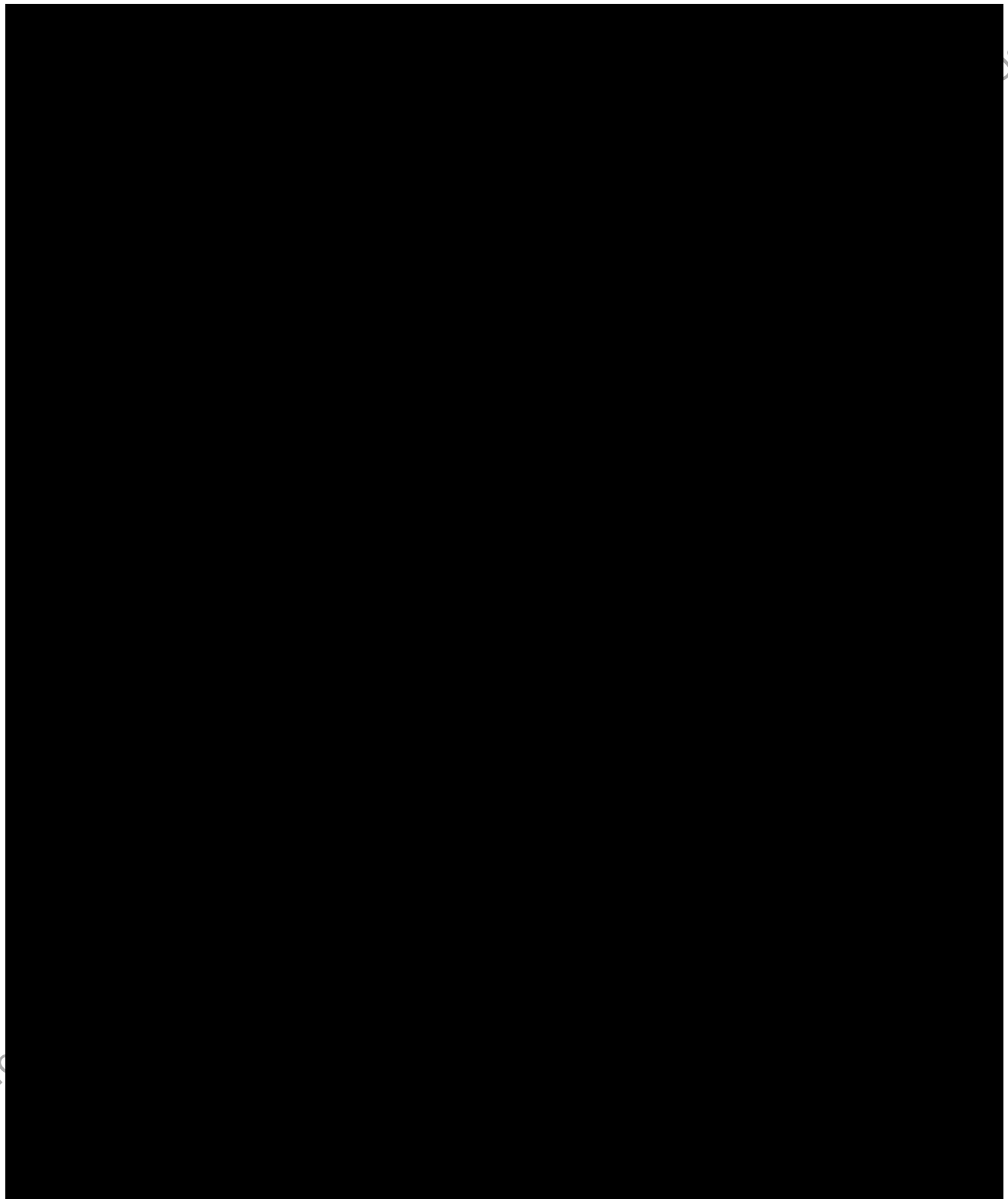
Brief summaries of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies are provided below. More detailed information is provided in the TAK-079 Investigator's Brochure (IB).

[redacted]

[redacted] Systemic exposures in the 13-week toxicity studies were considered adequate for assessment despite the formation of antidrug antibodies (ADA) observed more frequently at the lower doses, which negatively affected exposures likely via increased clearance. Assessments of local tolerance via either IV or subcutaneous (SC) dosing routes indicated no significant local injection site liabilities. Collectively, these data support the continued use of TAK-079 in humans.

4.2.1 [redacted]

[redacted]



4.3 Known and Potential Benefits and Risks to Patients with TAK-079

TAK-079 was administered only in healthy human subjects in the first-in-human (FIH) study (TAK-079_101). Only mild or moderate AEs were observed in the FIH study in healthy subjects. Therefore, clinical benefits and risks have not been assessed in the disease setting.

A summary of findings is discussed in Section 4.3.1. See details for precautions and restrictions in Section 8.7. Additional information regarding potential risks from treatment is provided in the TAK-079 IB.

4.3.1 Risks

Based on the mechanism of action of TAK-079, potential risks may include infusion or injection reactions, hematological effects, and serious infections.

4.3.1.1 Infusion and Injection Reactions

Infusion reactions are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents aimed at treating hematologic malignancies. Infusion reactions are less frequently associated with SC injection of these therapies. The 'true' clinical hypersensitivity reactions, antibody-mediated occur after repeat exposure. Symptoms of hypersensitivity range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Non-anaphylactic clinical hypersensitivity occurs within the first hour; however delayed responses were reported. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, bronchospasm, respiratory distress, and shock.

There are limited nonclinical and clinical data to date for TAK-079 (Section 4.2.1). Significant local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. However, patients in clinical trials receiving TAK-079 will be carefully monitored for signs and symptoms of IR, with appropriate management of these events. Depending on the severity of the reaction, management may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

See additional details for managing IRs in Section 8.8.1.

4.3.1.2 Cytokine Release Syndrome

CRS represents an important infusion reaction often associated with the use of monoclonal antibodies used in anti-inflammatory and antitumor therapies. CRS may occur in early phases of therapy, and often after the first infusion of the drug due to 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 also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting. Anaphylactoid reactions are characterized by chills, rigors, hypotension or hypertension, tachycardia, and/or loss of consciousness.

[redacted]

In the FIH study conducted in healthy human subjects, rarely-observed symptoms consistent with CRS of mild severity were reported particularly at higher doses, and they did not require dose adjustment or interruption. Potential occurrence of events associated with CRS will be carefully monitored in patients receiving TAK-079 and managed according to institutional guidelines.

[redacted]

4.3.1.3 Severe Cytokine Release Syndrome

Severe cytokine release syndrome (SCRS) is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumor lysis syndrome such as hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated lactate dehydrogenase, and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

4.3.1.4 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the NOAEL. Subjects in clinical studies of TAK-079 should be monitored closely, including testing of hematology parameters.

The important potential risk of these hematologic changes will be monitored throughout this clinical study, as described in Section 9.4.13 and Appendix A.

4.3.1.5 Serious Infections

In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

Subjects will be monitored for any signs and symptoms of the important potential risk of serious infections throughout this clinical study (see Section 8.8.3).

4.3.1.6 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 monoclonal antibody (mAb), the risk of drug-drug interactions is low.

4.3.1.7 ADA Interactions

ADA responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Strong positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeat-dose toxicity studies and at lower doses.

[redacted]

In the single-dose healthy subject study (TAK-079_101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these, 1 subject was treated in the 0.06 mg IV cohort and the remaining 4 subjects were treated with either 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity.

4.3.1.8 Pregnancy and Lactation

TAK-079 has not been administered to women who are pregnant or lactating. Dedicated fertility and embryo-fetal development toxicology studies have not been conducted with TAK-079. However, there were no TAK-079-related changes in organ weights or microscopic findings noted in the male and female reproductive tract of monkeys following administration for up to 13 weeks. Women of child bearing potential (WOCBP) may be enrolled in clinical trials with appropriate precautions to prevent pregnancy (additional details in Section 8.7).

At this stage of development TAK-079 should not be administered to women who are pregnant or breastfeeding.

4.3.1.9 Overdose

TAK-079 has been administered only to healthy subjects in the FIH study. To date, there is no experience with overdose. If an overdose does occur, close monitoring and supportive treatment as required are recommended.

4.3.2 Overall Benefit and Risk Assessment for This Study

The overall clinical benefits and risks of TAK-079 have not been determined.

Based on the mechanism of action of TAK-079, nonclinical data to date, as well as some exposure in healthy human subjects, risks of TAK-079 include but are not limited to IRs, CRS, hypersensitivity reactions, changes in hematologic parameters, and serious infections. Patients will be monitored closely for these risks in this clinical study.

4.4 Rationale for the Proposed Study

Although multiple therapies are available for patients with MM, this disease remains incurable; thus, significant unmet medical need exists for this patient population. Frequent relapses highlight a need for new therapies for patients in whom prior treatments have failed.

TAK-079 binds a partially distinct epitope of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab. Unlike daratumumab, TAK-079 does not bind to RBCs and platelets. Therefore, TAK-079 may possess higher tumoricidal activity than daratumumab because cytolytic effector activity is focused on CD38+ leukocytes/tumors and is not misdirected to RBCs and platelets. Consequently, TAK-079 may demonstrate higher potency (ie, activity at lower doses and exposures) and activity in

daratumumab-refractory tumors (ie, tumors expressing lower levels of CD38) and thus be more efficient at eliminating tumors.

In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed.

In summary, it is feasible to investigate administration of TAK-079 in patients with relapsed or refractory (r/r) MM.

4.4.1 Rationale for the Starting Dose of TAK-079

In the FIH study (TAK-079_101), TAK-079 was well tolerated after SC administration of single-doses ranging from 0.03 to 0.6 mg/kg.

To avoid unnecessary exposure of patients to sub-therapeutic doses while preserving safety, the starting dose for this study in patients with r/r MM will be 45 mg, the fixed-dose equivalent of 0.6 mg/kg (assuming a body weight of 75 kg), which was the highest SC dose administered in Study TAK-079_101. The 0.6 mg/kg dose was well tolerated in healthy human subjects in Study TAK-079_101 and demonstrated depletion of peripheral blood PBs, a surrogate for tumor cells.

TAK-079 is a mAb targeting CD38, which is a cell surface molecule that is constitutively expressed on plasma cells, PBs, and NK cells, and is induced on activated T cells and B cells [7]. Therefore, the anticipated elimination routes for TAK-079 are via proteolytic catabolism and intracellular degradation after binding to its target. Both of these clearance mechanisms are not thought to be significantly influenced by body weight. Additionally, the distribution volume of mAbs is generally limited to the volume of the blood and extracellular fluids, such that body composition is a less important determinant of distribution volume as compared with small molecule drugs [8]. For these reasons, body weight is not expected to have a clinically significant effect on the disposition of TAK-079, thereby supporting the investigation of fixed-dose administration.

The 45 mg starting dose of TAK-079 will be tested in 3 patients with r/r MM to assess the safety and tolerability of TAK-079 after multiple dose administration. TAK-079 will be administered using the same dosing schedule as the anti-CD38 antibody, daratumumab, which is approved for the treatment of patients with MM [5]. Specifically, TAK-079 will be administered once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), then once every 4 weeks until the patient experiences disease progression (PD), unacceptable toxicities, or withdrawal due to other reasons. The subsequent planned dose levels are 135, 400, 1200, and 1800 mg.

Escalation to a subsequent cohort may take place after the treatment in the first cycle of the previous (sequential) cohort has completed.

Additional details for dose escalation are provided in Section 8.3.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Phase 1 Primary Objective

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy in patients with r/r MM.

5.1.2 Phase 1 Secondary Objectives

The secondary objectives are:

- To investigate a potential maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

5.1.3 Phase 2a Primary Objective

The primary objective of the phase 2a portion of the study is to provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with r/r MM.

5.1.4 Phase 2a Secondary Objectives

The secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

5.1.5 Phase 1 and Phase 2a Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Phase 1 Primary Endpoints

The primary endpoints for phase 1 are:

- The number of patients with TEAEs overall and per dose level.
  - Patients with dose-limiting toxicities (DLTs) at each dose level.
  - Patients with Grade ≥3 TEAEs.
  - Patients with SAEs.
  - Patients who discontinue because of TEAEs.
  - Patients with dose modifications (delays, interruptions, dose reductions).
  - Clinically significant laboratory values, as determined by the investigator.
  - Clinically significant vital sign measurements, as determined by the investigator.

5.2.2 Phase 2a Primary Endpoint

The primary endpoint for phase 2a is:

- ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria [9,10].

5.2.3 Phase 1 Secondary Endpoints

The secondary endpoints for phase 1 are:

- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079 will be assessed for patients with MM:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria ([9,10]; Appendix E).
  - Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction ([[9,10]; Appendix E).
- Anti-TAK-079 antibody incidence and characteristics.

[redacted]

5.2.4 Phase 2a Secondary Endpoints

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause ([9,10];Appendix E).
- Overall survival (OS), defined as the time from the date of first dose to the date of death due to any cause.
- Time to response (TTR), defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

5.2.5 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients with r/r MM, and to provide a preliminary assessment of its activity against MM.

The phase 1 portion of the study will evaluate administration of TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs, dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, and review of concomitant medications.

The preliminary efficacy of TAK-079 will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [9,10]). In addition, the efficacy of TAK-079 will be assessed by measuring PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the study, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or withdrawal due to other reasons.

Phase 1 will consist of the following phases/periods: Screening, Treatment, and Follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing): Once-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.
- Follow-up Period (follow-up visit): Patients who discontinue for PD will be followed for 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after the last patient has received their last dose (last patient, last dose [LPLD]). All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

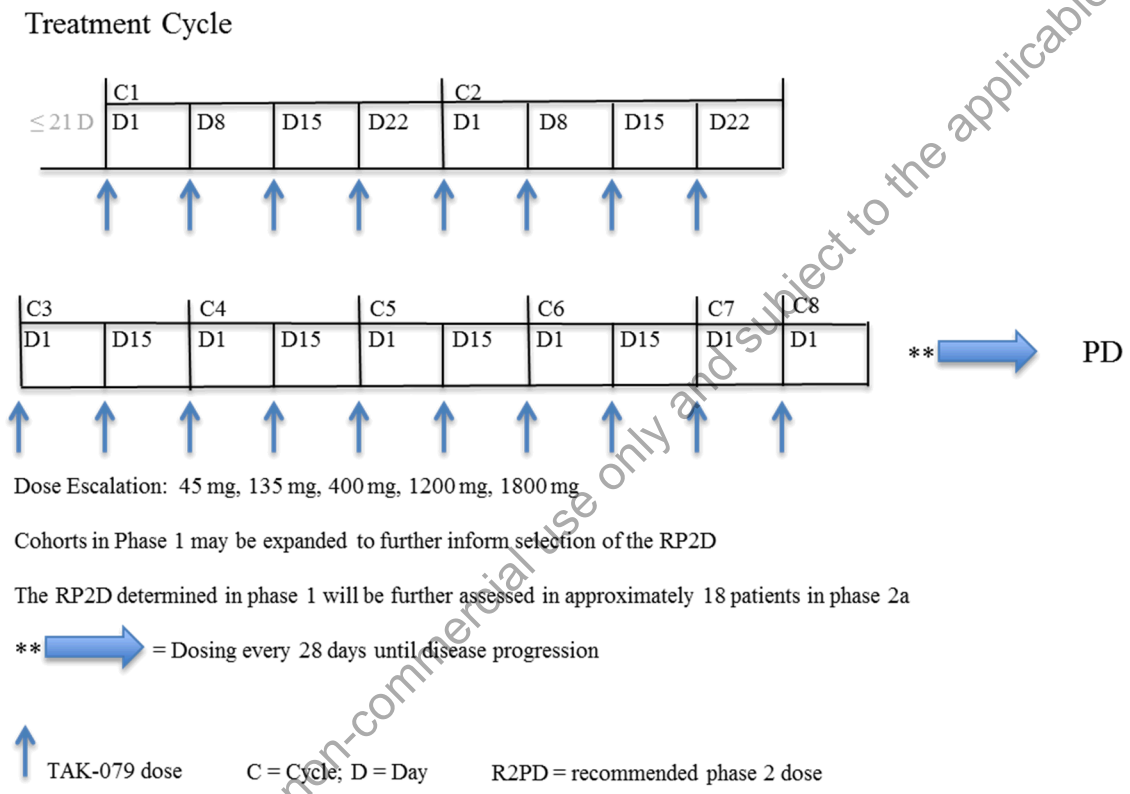
In phase 1, approximately 5 doses will be evaluated in ascending cohorts of 3-6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

[redacted]

It is expected that approximately 39 patients will be enrolled in total for phase 1 and 2a combined. The estimated duration of the study is approximately 48 months (4 years; Section 6.3).

Study procedures and assessments, with their time points, are shown in Appendix A. The study schematic diagram is shown in Figure 6.a.

Figure 6.a Overall Study Schematic Diagram



6.2 Number of Patients

For phase 1, approximately 21 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 18 patients are planned. Details on the definition of evaluable patients and sample size are given in Section 13.1.

The study is planned to be conducted in the United States in approximately 4 investigational centers for phase 1 and in a total of 6 investigational centers for phase 2a.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-079 until they experience PD as defined by IMWG for patients with MM ([9,10]; Appendix E), unacceptable toxicity, withdrawal of consent, death, termination of the study by the sponsor, until any other discontinuation criterion is met, or until 12 months after LPLD (additional participation details are provided in Sections 6.1, 8.4.3, 9.6, and 9.7).

Patients will be evaluated 30±7 days after the last dose of TAK-079 (follow-up visit) or before initiating subsequent systemic anticancer therapy, for detection of any delayed TEAEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final data cutoff for the clinical study report will be conducted 12 months after all patients have been discontinued from treatment or transferred to a long-term safety study, a single-patient investigational new drug application, or a similar program (Table 6.a).

6.3.3 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 From Final Clinical Study Report
Phase 1			
Primary:	Number of patients with TEAEs overall and per dose level: number of patients with TEAEs overall and per dose level; patients with DLTs at each dose level; patients with Grade ≥3 TEAEs; patients with SAEs; patients who discontinue because of TEAEs; patients with dose modifications (delays interruptions, dose reductions), clinically significant laboratory and vital sign values, as determined by the investigator	Includes assessments for patients with DLTs, Grade ≥3 TEAEs, SAEs, discontinuations because of TEAEs, dose modifications, and clinically significant laboratory values and vital signs.	1 year
Secondary:	Summary statistics for PK parameters: C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year

Endpoint	Definition	Maximum Time Frame From Final Clinical Study Report
Secondary: Preliminary evaluation of antitumor activity of TAK-079: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary: Preliminary evaluation of antitumor activity of TAK-079: MR	Proportion of patients who achieved a minimal response, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary: Anti-TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year
Phase 2a		
Primary: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary: DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.	Includes assessments for patients with DLTs and other TEAEs, dose modifications, treatment discontinuations, clinically significant laboratory values, and vital signs.	1 year
Secondary: Summary statistics for PK parameters of C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).See Section 13.1.4.	1 year
Secondary: Anti-TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year
Secondary: MR	Proportion of patients who achieved MR, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary: DOR	Time from the date of the first documentation of response to the date of the first documented PD. See Section 13.1.3.	1 year

[redacted]

Endpoint	Definition	Maximum Time Frame From Final Clinical Study Report
Secondary: PFS	Time from the date of the first dose until the earliest date of PD, or the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: OS	Defined as the time from the date of first dose to the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: TTR	Time from the date of the first dose to the date of the first documentation of response (PR or better). See Section 13.1.3.	1 year

DLT=dose-limiting toxicity; DOR=duration of response; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTR=time to response.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 48 months (4 years).

[redacted]

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. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 [11].
3. Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079 (Table 7.a):

Table 7.a Required Washout Periods for Previous Treatments or Procedures Prior to Administration of TAK-079

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	30 days
Antibody therapy (including anti-CD38)	120 days
Corticosteroid therapy (a)	30 days
Autologous transplantation	90 days
Radiation therapy	30 days
Major surgery	30 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.

4. Patient has adequate organ function as determined by the following laboratory values (Table 7.b):

Table 7.b Laboratory Criteria for Determining Adequate Organ Function for Study TAK-079-1501 Eligibility

Laboratory Parameter	Acceptable Laboratory Criteria
Absolute neutrophil count (a)	≥1000/mm^3 (≥1.0×10^9/L); ≥750/mm^3 (≥0.75×10^9/L) maybe acceptable for patients with >50% of plasma cells in bone marrow after discussion with sponsor
Platelets (a)	≥75,000/mm^3 (≥75×10^9/L); a 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
Hemoglobin	≥7.5 g/dL (it is not permissible to transfuse a subject to reach this level)
Creatinine clearance	≥30 mL/min (Cockcroft-Gault)
Total serum bilirubin	≤1.5×ULN; an exception for patients with Gilbert's syndrome may be granted after discussion with the sponsor
Liver transaminases (ALT/AST)	≤2.5×ULN

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.
(a) Without ongoing growth factor or transfusion support for at least 1 week before Day 1.

5. Female patients who:

- Are WOCBP must not be pregnant or lactating.
- 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 at least 30 days or 5 half-lives after the last dose of study drug, whichever time period is longest, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
8. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.
9. Requires additional therapy, as determined by the investigator.
10. Documentation of r/r MM as defined by the IMWG criteria (Appendix E; [9,10]).
11. For patients with MM, measurable disease defined as one of the following:

- Serum M-protein ≥500 mg/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.

[redacted]

12. Previously received at least 2 lines of standard therapy (including both an IMiD and a PI), and is either refractory to or intolerant of at least one of these regimens. Prior treatment with an anti-CD38 mAb is allowed; however, CD38 expression must be significantly expressed on target cells for this mechanism of action to be effective.
13. In the phase 2a portion of the study, patients with MM must also have been refractory to at least 1 anti-CD38 mAb therapy at any time during treatment.

NOTE:

- Refractory is defined as at least a 25% increase in M-protein or PD during treatment or within 60 days after cessation of treatment.
- A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of PD, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease [9].

7.2 Exclusion Criteria

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

1. Sensory or motor neuropathy of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 [12].
2. Patients who have received allogeneic stem cell transplant.
3. Patients who have received anti-CD38 antibody therapy and do not fulfill a 120-day washout period before receiving TAK-079.
4. Not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE Grade ≤1 or baseline.
5. Congestive heart failure (New York Heart Association) Grade ≥II; cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.
6. History of acute myocardial infarction within 5 months before enrollment or ECG abnormalities during the screening period that are deemed medically relevant by the investigator.
7. QT interval corrected by the Fridericia method >480 msec (Grade ≥2).

[redacted]

8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume <50%, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.
9. History of stroke or intracranial hemorrhage within 12 months of randomization; patients requiring anticoagulation therapy for any indication should be discussed with the medical monitor before screening.
10. Active autoimmune disease including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or any chronic condition requiring a higher corticosteroid systemic equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped 30 days prior to randomization; exceptions may be made for corticosteroids prescribed specifically for management of MM symptoms after discussion with the medical monitor.
11. History of myelodysplastic syndrome or another malignancy other than MM, except for the following: any malignancy that has been in complete remission for 3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, or asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year before the start of study therapy.
12. Clinical signs of CNS involvement of MM.
13. Female patients who are pregnant with a positive serum pregnancy test or lactating during the screening period, or a positive urine pregnancy test on Day 1 before the first dose of study drug, if applicable.
14. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, active HIV, or cytomegalovirus (CMV) infection.
16. History of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation. This includes patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction.
17. The patient is currently participating in another antimyeloma or antileukemia clinical study, or has participated in another investigational clinical trial within the past 4 weeks prior to randomization.

[redacted]

18. Patients who are not able and/or willing to comply with the study requirements, rules, and procedures.
19. POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, or IgM myeloma.

[redacted]

8.0 STUDY DRUG

8.1 Study Drug Administration

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

8.1.1 Premedication

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor) is optional for Cycle 1, Day 1.

NOTE: Patients with a higher risk of respiratory complications (eg, patients with COPD who have a forced expiratory volume in 1 second of <80%; and patients with asthma) will be treated with post-injection medication consisting of the following:

- An antihistamine (diphenhydramine or equivalent) on the first and second days after all injections,
- A short-acting β_2 adrenergic receptor agonist, such as salbutamol (albuterol) aerosol, and
- Control medications for lung disease (eg, inhaled corticosteroids with or without long-acting β_2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol with or without inhaled corticosteroids for patients with COPD).

Premedication will be mandatory in phase 1. The decision to premedicate in phase 2a will be determined based on data from phase 1.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

8.1.2 TAK-079 Formulation and Administration

The strength of the TAK-079 drug product for SC use in the current study (TAK-079-1501) is 100 mg TAK-079 in 1 mL (100 mg/mL). The drug product is supplied in clear borosilicate glass vials (see additional details in Section 8.10).

After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL), injected every 30 minutes until the full scheduled dose has been administered.

Patients may receive low-dose methylprednisolone (≤ 20 mg) for the prevention of delayed injection related reaction, as clinically indicated.

Refer to the Pharmacy Manual for detailed instructions regarding preparation of each dose.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [12]. These criteria are provided in the Study Manual. DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with TAK-079.

- Nonhematologic TEAEs of NCI CTCAE Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - Asymptomatic laboratory changes (other than renal and hepatic laboratory values, and Grade 4 lipase/amylase) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
  - Grade 3 nausea/vomiting that can be managed subsequently with anti-emetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 72 hours.
  - Grade 3 elevation of ALT or AST that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms.
- Hematologic TEAEs of NCI CTCAE Grade ≥4 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis clearly unrelated to the underlying disease (eg, negative direct Coombs test) will be included in the definition of DLT.
  - Grade 3 low platelet or higher count with clinically meaningful bleeding will be included in the definition of DLT.
  - Grade 4 low platelet count of duration <2 weeks will not be included in the definition of DLT.
  - Grade 4 lymphopenia will not be included in the definition of DLT.

[redacted]

- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a DLT.

For the purpose of dose escalation, DLTs are those events meeting the criteria above that occur before Cycle 2 Day 1 administration. TEAEs meeting DLT definitions occurring in later cycles will determine the suitability of the MTD as the RP2D.

Dose and schedule modifications for toxicity are described in Section 8.4.

8.3 Dose-Escalation Design and Criteria

8.3.1 Dose Level(s):

Patients will be enrolled in cohorts of 3 to 6, following an adaptive dose-escalation design.

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 400 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D.

[redacted]

Phase 2a

In the absence of DLT, the dose that will be administered in the subsequent phase 2a portion of the study will be based upon a comprehensive review of available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study.

[redacted]

8.3.2 Escalation Schema

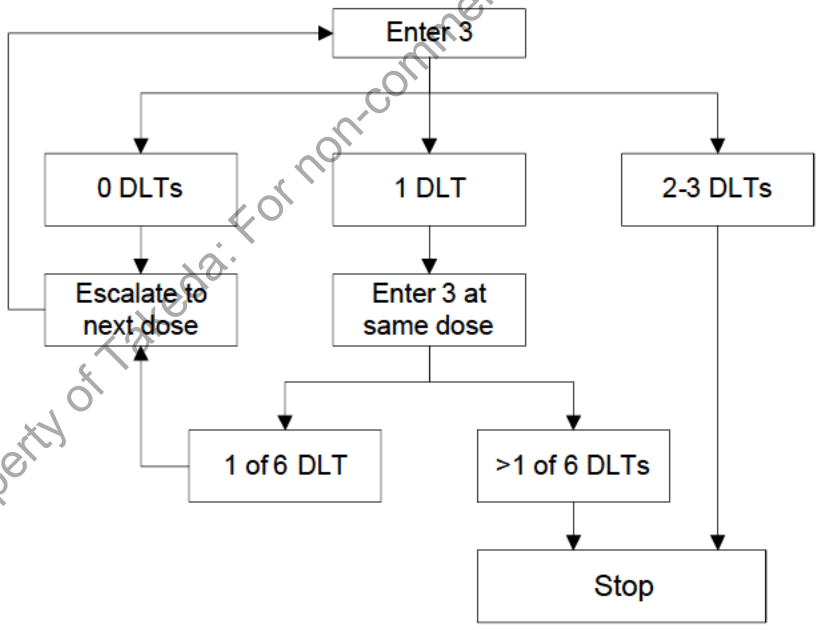
The Bayesian Logistic Regression Modeling (BLRM) method with overdose control will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

The following rules will apply only for this initial dose level:

- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
  - If no additional patient in the expanded cohort of 6 exhibits a DLT, then the dose may be escalated for the next cohort of 3 patients (pending approval following review of available safety data).
  - If a second (or more) patient in the expanded cohort of 6 exhibits a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped (pending BLRM approval following review of available safety data).
- If 2 or more patients in a cohort of 3 patients exhibit a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped.

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm for the first cohort.

Figure 8.a Dose-Escalation Scheme for Cohort 1



DLT=dose-limiting toxicity.

[redacted]

Once the dose is escalated above the starting dose level, BLRM will be used for all subsequent dose recommendations, along with consideration of other safety, clinical, PK, [redacted] data. More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or [redacted].

Before initiating the dosing of the next cohort, when safety data are available for all patients in the current cohort, key safety data will be reviewed and evaluated by the study team consisting of sponsor representatives and investigators who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, changes to the dose-escalation scheme or dose schedule (dosing interval) may be considered. All decisions will be documented in writing. Any decision to modify the dose-escalation scheme (with the exception of testing intermediate dose levels) or dose schedule will be communicated to institutional review boards (IRBs), and the protocol will be amended accordingly.

8.4 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for TAK-079 on the basis of the type and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

8.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with TAK-079 will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- Absolute neutrophil count must be $\geq 1000/mm^3$.
- Platelet count must be $\geq 75{,}000/mm^3$.
- For therapy to resume, toxicity considered to be related to treatment with TAK-079 must have resolved to Grade ≤ 1 or baseline, or to a level considered acceptable by the physician. If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If there is a delay of a subsequent cycle longer than 2 weeks because of a drug-related AE, 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. TAK-079 dosing may be continued at the previously established safe dose level or below.
- For TAK-079 injections within the same cycle, the decision of holding treatment is left to the investigator's discretion based on clinical and analytical data, and also based on the toxicity that the patient experienced with previous injections in the same cycle. The investigator should differentiate between acute toxicity (like an IR) from which the patient is recovered at the time of the next injection, and subacute toxicity (for example, neutropenia) that might be worsened

upon another injection if it is not on a clear recovery path. If the dose cannot be administered on the scheduled day, the patient can be reviewed at the investigator's discretion in the following 48 hours. If TAK-079 cannot be administered within a cycle in this 48-hour window, the dose will be missed and the patient scheduled for the next administration per the Schedule of Events (SOE; Appendix A).

8.4.2 Criteria for Dose Reduction

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held, may have their dose reduced, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, 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 study drug may be treated as per local standard of care, dose-modifications, interruptions and permanent discontinuations may be discussed upfront with the medical monitor.

Table 8.a provides general dose modification recommendations. When the dose of TAK-079 is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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. See details for managing specific AEs in Section 8.8.

[redacted]

Table 8.a Dose Modification Recommendations for TAK-079 Toxicities

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same or a reduced dose is at the discretion of the investigator. 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, then restarted at the same dose or, depending on the toxicity, at the previous safe dose level or below.
Grade 3 AEs	Hold TAK-079 until resolution to Grade ≤1 or baseline, then resume treatment at either the same dose or a reduced dose level at the discretion of the investigator.
Grade 4 (life-threatening) AEs	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor. Treatment may be restarted at a reduced dose level or below when toxicity recovers to Grade ≤1 or baseline.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment can be resumed at a reduced dose level after resolution of AEs to Grade ≤1 or baseline.

AE=adverse event.

When a dose reduction occurs, the TAK-079 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-079 can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-079 because of AE are generally recommended.

If dose-reduction is not possible because the lowest dose-level has already been reached, treatment may be permanently discontinued.

The dose of TAK-079 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

8.4.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification)

TAK-079 should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that re-treatment of the patient could be dangerous. For Grade 4 (life-threatening) TEAEs, consider permanently withdrawing the patient from the study,

except when the investigator determines that the patient is receiving clinical benefit, there are opportunities to provide supportive care to mitigate risk for the Grade 4 event to reoccur, and this approach (ie, the specific situation and mitigation plan) has been discussed with the sponsor. In these circumstances, treatment may be restarted at the previously safe dose level or below when toxicity recovers to Grade ≤1 or baseline.

If the next cycle of TAK-079 is delayed for >14 days because of TAK-079–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 occurs, the end of treatment (EOT)/early termination visit should be completed and the follow-up visit should occur within 30 (±7) days after the last administration of TAK-079. Additional details for study treatment discontinuation are provided in Section 9.7.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy and radiation therapy for the disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor's medical monitor and once PD is ruled out.
- Systemic corticosteroid use >10 mg/day (prednisone or equivalent).
- Live vaccines.
- Any investigational agent other than TAK-079, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.

8.6 Permitted Concomitant Medications and Procedures

- All necessary supportive care consistent with optimal patient care will be available to patients as necessary. All blood products and concomitant medications received from the first dose of the study drug regimen until 30 days after the final dose will be recorded in the electronic case report forms (eCRFs).
- The following medications and procedures are permitted while the patient is receiving the study drug:
  - Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent).
  - Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice.
  - Transfusions with RBCs and platelets as clinically indicated; localized radiation for pain management for osteolytic lesions.
  - Concomitant treatment with bisphosphonates will be encouraged for all 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. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.

- Topical or inhaled steroids and short-acting β_2 adrenergic receptor agonists (eg, for the treatment of asthma) are permitted.
- Nonresorbable corticosteroids (eg, budesonide).
- Plasmapheresis.

8.7 Precautions and Restrictions

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

NSAIDs should be avoided with impaired renal function given the reported NSAID-induced renal failure in patients with decreased renal function.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-079 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following:

- WOCBP must not be pregnant or lactating.
- 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 5 half-lives after the last dose of study drug (whichever is longer), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

[redacted]

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium, and uric acid levels must be performed. Patients with tumor lysis syndrome should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis as indicated).

8.8 Management of Specific Adverse Reactions

8.8.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of an IR, blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

For additional details, refer to Section 9.4.15.3.

8.8.2 Handling of Low Platelet Counts

Treatment decisions will be based on patient platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled treatment to be postponed or to be permanently discontinued. If at any time the platelet count is less than 10×10^9/L, or if the patient shows a bleeding tendency considered to be due to thrombocytopenia occurring after initiation of TAK-079 treatment, the patient should be withdrawn from TAK-079 treatment. Platelet transfusion and daily monitoring of platelet counts are recommended. These patients should be considered as having experienced an SAE.

8.8.3 Risk of Infection

The intended mechanism of action of TAK-079 may involve reduction of the subject's immune response. Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis treatment may be initiated as clinically indicated, as

determined by the investigator. Patients during the study should be followed closely for signs and symptoms of infection and treated as clinically indicated.

Until more clinical experience is gained with the use of TAK-079, it is prudent to avoid situations that may place subjects at increased risk of infection.

8.8.4 Transfusion Risks

Blood samples from patients being treated with TAK-079 may show pan reactivity during pretransfusion testing. To facilitate the provision of blood components for such patients, it is recommended that a baseline phenotype or genotype be established before starting treatment with TAK-079. Patients should keep this information in case future transfusions are needed. If a patient requires RBC phenotyping after the start of TAK-079 treatment, dithiothreitol treatment of the patient's RBCs should be performed, in case of preexisting positivity to standard tests.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

[redacted]

8.11 Preparation, Reconstitution, and Dispensation

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

TAK-079 is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling TAK-079.

[redacted]

8.12 Packaging and Labeling

Supplies of TAK-079 will be labeled according to the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

8.13 Storage, Handling, and Accountability

8.13.1 Storage and Handling

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label.

During shipping, vials will be protected from light and maintained below -15°C (5°F). Each TAK-079 shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

The investigator is responsible for ensuring that deliveries of TAK-079 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Detailed dosage preparation instructions are provided in the Directions for Use section of the Pharmacy Manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the Pharmacy Manual.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the Pharmacy Manual.

8.13.2 Accountability and Destruction of Sponsor Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator must maintain 100% accountability for all study medication (TAK-079) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative, otherwise uninvolved with study conduct, will review the subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication. This review will be documented at the site.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Empty, partially used, and unused TAK-079 will be disposed of, retained, or returned to the sponsor or designee.

The investigator must maintain a current inventory (Drug Accountability Log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and subjects' use

records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

8.14 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned using an 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 numbers (MED IDs) 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.

[redacted]

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory, and any additional clinical laboratories, the coordinating investigator for each member state/country, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC). The screening period for this study is 21 days.

9.3 Treatment Group Assignments

All patients will receive open-label treatment with TAK-079 as indicated in respectively assigned treatment cohorts.

9.4 Study Procedures

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. This includes initial diagnosis date and MM staging at initial diagnosis using the International Staging System and Salmon-Durie Staging. Before dosing, the investigator should select the International Staging System, which should be consistently used throughout the study.

Known cytogenetic alterations should also be collected. Prior treatment regimens, with each treatment duration (start and stop dates), and the best response obtained with each therapy should be recorded. Refractoriness to previous treatments should be collected following IMWG criteria

(Appendix E). Confirm that the patient's current medical status does not include active chronic HBV, HCV, CMV, or HIV infection.

For patients who have received previous anti-CD38 therapy, the worst grade of infusion-related reactions should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured during the Screening Visit only. Weight will be measured on Day 1 of each treatment cycle, as indicated in Appendix A.

9.4.6 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital sign measurements will be made before TAK-079 injection, and include supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position). All measurements should be performed in the same initial position, including heart rate and body temperature.

Blood pressure will also be measured before each injection, and at any time the patient complains of symptoms consistent with IR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Vital signs will be measured at the visits specified in the SOE (Appendix A). 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 10.2.

9.4.7 Eligibility Criteria

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.

9.4.8 Pregnancy Test

WOCBP must have 2 negative pregnancy tests (human chorionic gonadotropin >5 mI/mL) prior to starting study drug. A serum pregnancy test will be used during the screening period (within 10 to 14 days before the start of study drug). A serum pregnancy test must also be performed at baseline (within 24 hours before the start of study drug). A WOCPB is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential)

for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

During the study, if a menstrual period is delayed, absence of pregnancy in WOCBP must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study upon request by an IRB or if required by local regulations.

A urine pregnancy test is required in WOCBP at designated treatment visits (Appendix A) and also at the follow-up visit.

9.4.9 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had within 21 days before TAK-079 administration and up to 30 days after the last dose of TAK-079 (or the start of subsequent anticancer therapy, whichever occurs first) will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF. See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.10 AEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.4.11 Enrollment

A patient is considered to be enrolled in the study at the first injection.

Procedures for completing the enrollment information are described in the Study Manual.

9.4.12 ECG

A single ECG will be collected at the screening visit for assessment of eligibility. A qualified person will interpret the ECG.

Time-matched triplicate 12-lead ECGs and PK samples will be collected in this study during Cycles 1 and 2 as specified in Appendix B. Although the number of scheduled ECG measurements will not be increased, the timing may be changed if emerging data indicate that an alteration in the ECG schedule is needed. Triplicate ECGs will be recorded electronically and transmitted to a central vendor for storage.

The triplicate ECG measurements should be completed before the PK blood draw. Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window. It is recommended that patients refrain from eating or limit

themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement.

Single, 12-lead ECGs will be administered at all other designated visits (ie, after Cycle 2), as specified in Appendix A.

Any ECG finding that is judged by the investigator as clinically significant (except at the Screening Visit) will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally (includes the direct and indirect Coomb's tests). Exceptions are discussed below.

Handling of clinical laboratory samples will be outlined in the Study Manual. [redacted] and immunogenicity (ADA and potential neutralizing antibodies [NAB]) assessments are to be performed centrally.

[redacted]

Decisions regarding eligibility for this study may be made using local laboratory determinations in the dose-escalation portion of phase 1 of this study. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

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

[redacted]

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
ANC	Albumin	Creatinine clearance
Hematocrit	ALP	CRP
Hemoglobin	ALT	Glucose (nonfasting)
Platelet (count)	AST	GGT
Reticulocyte count	Bilirubin (total)	LDH
RBC count	BUN	Phosphate
WBC count	Calcium	Potassium
WBC with differential	Chloride	Sodium
Coagulation panel	CO2 (bicarbonate)	Total protein
	Creatinine	Urate (uric acid)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=serine aminotransferase; BUN=blood urea nitrogen; CO_2=carbon dioxide; CRP=C-reactive protein; GGT=Gamma glutamyl transferase; LDH=lactate dehydrogenase RBC=red blood cell; WBC=white blood cell.

Table 9.b Clinical Urinalysis Tests

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

For estimation of creatinine clearance, the Cockroft-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.

9.4.13.2 Prestudy Prognostic Risk Assessment

A blood sample will be collected for serum β2 microglobulin at screening to assess patient disease status. Results will be analyzed locally.

9.4.14 Disease Response Assessments

Patients will be assessed for disease response according to the IMWG for MM ([9,10]; Appendix E).

Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079.

[redacted]

Imaging tests as specified in Appendix A are to be performed as defined below or when there is a clinical suspicion of progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase before treatment, at the beginning of Cycles 2, 4, 7, 13, 19, 25, and every 6 cycles thereafter until PD or intolerance.

CR should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.

Note that to determine a response of sCR, BMA immunohistochemistry or immunofluorescence for kappa:lambda ratio, as well as serum FLC assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

PD may be confirmed per standard clinical practice at the site. Local laboratory results may be used to confirm PD.

9.4.14.1 Computed Tomography/Magnetic Resonance Imaging

For patients with documented extramedullary disease, a whole body x-ray, positron emission tomography–computed tomography (PET-CT) scan, computed tomography (CT) scan (includes low-dose CT), or magnetic resonance imaging (MRI) scan will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, that image be used as baseline and does not need to be repeated as part of screening) as needed for evaluation of disease. If disease is documented, then a repeat PET-CT scan, CT scan, or MRI scan should be performed as required to document response or PD.

Scans will be performed at screening and at the EOT/early termination visit. All treatment phase and follow-up scans should use the same imaging modality used at screening.

Surveys (x-ray, CT, or MRI) may also be performed at the investigator's discretion, eg, in case of bone pain. The screening scan may be performed up to 21 days before first dose of TAK-079. Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.4.14.2 Quantification of Immunoglobulins

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained at the screening visit, predose on Day 1 of every cycle, and at the follow-up visit. Analysis of Ig will be performed locally.

9.4.14.3 Quantification of M-Protein

A predose blood and 24-hour urine sample will be obtained at the screening visit, Day 1 of every cycle, and at the follow-up visit. Urine sampling at designated timepoints is required only if urine M-protein is measurable at Day 1.

The samples will be tested locally. M-protein in serum and urine will be quantified by SPEP and UPEP.

[redacted]

9.4.14.4 Serum FLC Assay

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, and at the follow-up visit for the serum FLC assay (including quantification of kappa and lambda chains and ratio). Blood samples will be analyzed locally.

9.4.14.5 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, at the follow-up visit, and to confirm CR. Immunofixation testing will be performed in a local laboratory.

9.4.14.6 BMAs

BMAs will be taken during the screening period and at the beginning of designated study visits at Cycles 2, 4, 7, and every 6 cycles thereafter (ie, 13, 19, 25, etc.) until PD or intolerance, as described in Appendix A for the BMA measurements. Requirements for BMA assessments to confirm disease responses are defined at the beginning (Section 9.4.14).

Central Laboratory Evaluations

Molecular Analyses and Cytogenetics
The sample of BMA obtained at screening will be used for molecular analyses and for evaluation of cytogenetics. For response assessment purposes, when a CR is suspected on laboratory values, a BMA is required to confirm a CR as per routine clinical practice. At the time of this procedure, 1 sample is analyzed locally for evaluation of disease, while a separate aspirate sample must be sent directly to the central laboratory on the day of collection in accordance with the procedures outlined in the Study Manual/Laboratory Manual.

It is also highly encouraged (optional) to perform an aspiration procedure for the same purpose in patients who achieve PR as best response.

An aspirate for molecular analysis will also be collected at the time of disease relapse. This sample will be collected at the time of PD confirmation, before starting a new therapy, and will be sent to the central laboratory for analysis.

Local Laboratory Evaluations

Disease Assessment

A BMA will be obtained at screening for disease assessment and at any time a BMA sample is obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally. Determination of the kappa/lambda ratio by immunohistochemistry or immunofluorescence should be performed to assess for sCR when CR has been documented.

A standard BMA drawn before consent is acceptable provided it is collected within 5 weeks prior to the first dose.

[redacted]

Cytogenetics

If a sufficient sample is available at screening, an additional BMA or bone marrow sample may also be submitted for cytogenetic evaluation to be analyzed locally, according to local standards, if the site has the capability to perform the analysis. These analyses should be performed at screening using fluorescence in situ hybridization and/or conventional cytogenetics (karyotype). The central laboratory cytogenetic results will be used for study analysis, whereas local laboratory cytogenetic results (where available) will be used only in instances when central laboratory results are not available.

9.4.15 [redacted], PK, [redacted], and Immunogenicity Samples

9.4.15.1 Primary Specimen Collection for PK, [redacted], and [redacted] Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix B for the measurement of serum concentrations of TAK-079 and in Appendix A for [redacted].

The primary specimen collection is presented in Table 9.c. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for TAK-079 PK	Serum	PK measurements	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
Serum sample for immunogenicity	Serum	Immunogenicity assessments	Mandatory
Serum sample for direct and indirect Coomb's Test	Serum	Immunogenicity assessments	Mandatory

PK=pharmacokinetics.

[redacted]

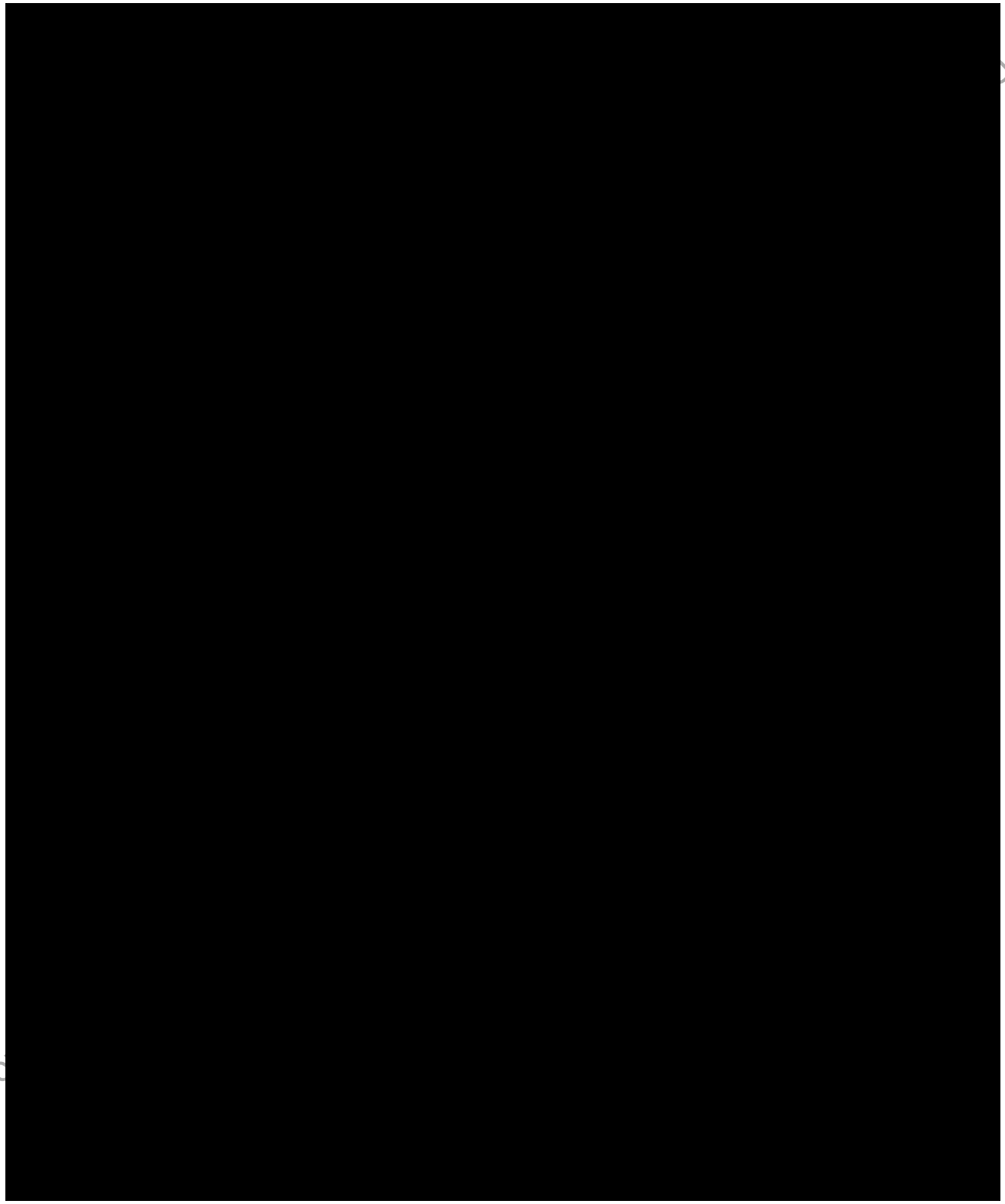
9.4.15.2 PK Measurements

Serum samples for the measurement of concentrations of TAK-079 will be collected at multiple time points as specified in Appendix B.

The timing, but not the total number, of samples may be modified during the study on the basis of emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079. If multiple SC injections are required in order to administer the intended dose, postdose PK assessments are to begin after administration of the final injection.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual.

9.4.15.3 [redacted]



9.4.15.4 Immunogenicity Assessments

ADA Assessment

Serum samples for the assessment of anti-TAK-079 immunogenicity will be collected at the study visits specified in Appendix A. A blood sample will be collected before administration of TAK-079 (ie, prior to dosing on Day 1; baseline value), then subsequently before TAK-079 dosing at each designated visit (postbaseline values), and at visits for any patient who experiences a TEAE considered by the investigator to be consistent with hypersensitivity/IR.

A sample will initially be screened for ADA titer. If a sample is detected as ADA positive, it may be assessed for neutralizing activity.

Direct and Indirect Coomb's Testing

Serum samples for direct and indirect Coomb's testing will be collected at time points specified in Appendix A. These tests will be performed locally.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered as having completed study treatment if they discontinued study drug for any reason as outlined below in Section 9.7.

9.6 Completion of Study (for Individual Patients)

Patients will receive TAK-079 until they experience PD, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor (see additional details in Section 9.8).

Patients will have a follow-up visit 30 days after the last dose of study drug or prior to the start of subsequent alternative anticancer therapy, to permit the detection of any delayed AEs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

Patients will be followed every 12 weeks for OS until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

It is anticipated that the duration of the study will be approximately 48 months (4 years).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.
- Withdrawal by patient.
- Female patient has confirmed pregnancy.

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

- AE/SAE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.

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

In phase 1, patients who do not receive 4 injections of TAK-079 within the 28-day (±2) treatment window or the Day 29 (ie, Cycle 2 Day 1) assessment for reasons other than a DLT will be replaced. In phase 2a, patients who receive 1 or more injections of study drug will not be replaced.

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

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 by patient (mandatory immediate discontinuation of study agent).
- Death.
- PD.

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

9.9 Study Compliance

Study drug will be administered 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.

[redacted]

9.10 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than progressive disease will continue to have progression-free follow-up visits (additional details in Section 9.6). Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD, whichever occurs first.

Patients who stop treatment due to PD will continue to have OS visits. Patients will be followed every 12 weeks for OS after documented PD until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD, 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.

See the SOE (Appendix A) for appropriate assessments during follow-up.

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

[redacted]

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 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 4.03, effective date 14 June 2010 [12]. 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 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 <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 and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

Cognizant
United States and Canada
Toll-free fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

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

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

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [12]. 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.

SAEs:

- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 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 caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

[redacted]

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

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

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

Product	Call Center	Phone Number	E-mail	Fax
TAK-079	DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2)

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

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

[redacted]

11.0 STUDY-SPECIFIC COMMITTEES

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

[redacted]

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain

essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

[redacted]

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of TAK-079.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-079 and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of TAK-079.

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, and DOR.

[redacted]

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient dosing data and TAK-079 concentration-time data to permit the calculation of PK parameters.

Immunogenicity analysis set: The immunogenicity analysis set will include those patients from the safety population who have baseline and at least one postbaseline sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. 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 if necessary.

[redacted]

13.1.3 Efficacy Analysis

Data from any efficacy assessments performed after the specified follow-up time will not be collected on the eCRF; if such data are collected, these data will not be analyzed.

The preliminary efficacy of TAK-079 for MM will be evaluated by measuring the ORR defined as the proportion of patients who achieved a PR or better during study; the composition of sCR, CR, very good partial response (VGPR), and PR as defined by the IMWG Uniform Response Criteria (see Appendix E).

In addition, the efficacy of TAK-079 will be assessed in patients by measuring DOR, PFS (PD will be defined by IMWG criteria), and 1-year OS. TTR will also be measured.

13.1.4 PK Analysis

PK parameters will be estimated using noncompartmental analysis methods. Parameters will be calculated for individual patients included in the PK analysis set using the TAK-079 concentration-time data. The calculated PK parameters will include, but not be limited to, C_{max}, t_{max}, and AUC_{last} (as permitted by the data).

PK parameters will be summarized using descriptive statistics. Individual TAK-079 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 PK data collected in this study may also contribute to future population PK analyses of TAK-079. These population PK analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Similarly, the time-matched PK and triplicate ECG data collected in this study may contribute to future concentration-QT interval corrected for heart rate (QTc) analyses. These analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the concentration-QTc analysis will be separately defined, and the results will be reported separately.

13.1.5 [redacted]

[redacted]

13.1.6 Immunogenicity Analyses

TAK-079 immunogenicity will be analyzed using the immunogenicity analysis set. The proportion of patients with positive ADA (transient and persistent) will be summarized, and the proportion of patients in phase 2a with positive neutralizing ADA during the study may be

[redacted]

summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined. NABs may also be assessed in patients.

The immunogenicity of TAK-079 will be assessed by determining anti–TAK-079 antibody incidence and characteristics (eg, titer, transiently, and persistently ADA; and possible neutralizing activity). Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-079 antibodies on the PK profile, drug efficacy, and clinical safety will be evaluated, if possible.

13.1.7 Safety Analysis

The safety and tolerability of TAK-079 will be assessed by the recording and analysis of TEAEs (NCI CTCAE version 4.03; [12]), vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, and concomitant medications.

TEAEs will be summarized using the safety analysis set and will be coded using the MedDRA. Data will be summarized using preferred term and primary system organ class.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

It is expected that approximately 39 patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately 18 patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with r/r MM.

An adaptive approach with BLRM will be used for dose escalation. BLRM implements dose escalation with overdose control principle [13,14] that informs dose-escalation decisions and MTD/RP2D estimation, along with consideration of other safety, clinical, PK, [redacted] data.

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

$$\text{logit}(\pi_i) = \log(\alpha) + \beta \log\left(\frac{dose_i}{dose_{ref}}\right), \qquad \alpha > 0, \beta > 0$$

where π_i is the DLT rate for dose i and $dose_{ref}$ is a reference dose. A quantile-based, non-informative, bivariate normal prior will be used for ln(α) and ln(β). This prior will be assigned based on prestudy estimates of the DLT rate at each dose level, as described in Neuenschwander, et al. [13].

[redacted]

The model will be updated after each group of 3 patients is enrolled in the current dose level cohort. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

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

The next recommended dose will be selected as described in Section 8.3.2.

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on BLRM, with consideration for other safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile. The simulation to evaluate the sample size is performed based on possible dose level range (45, 135, 400, 1200, and 1800 mg). The simulation is performed based on 6 scenarios of the assumed true DLT rates at the different dose levels (45, 135, 400, 1200, and 1800 mg), representing various distributions of toxicity across dose levels, detailed as shown in Table 13.a. The curve of the dose-DLT relationship becomes steeper and MTD is reached earlier from Scenario 1 to Scenario 6. The quantile-based, non-informative, bivariate normal prior of ln(α) and ln(β) is determined based on prestudy estimates of DLT rate (0.02, 0.05, 0.10, 0.20, and 0.30) at various dose levels (45, 135, 400, 1200, and 1800 mg). Table 13.b shows [redacted]

In Scenario 1, the probability of recommending the highest dose level (1800 mg) is 100% when there is close to a 0 true DLT rate with the current doses. In Scenario 1, the average number of patients required is approximately 18 with 0 DLTs expected on average. Similar results are observed in the Scenario 2 where the true DLT rate increases very slowly and none of the target true DLT occurs at any of the current dose levels. The true DLT rates in Scenario 3 increases faster than in Scenario 1 and 2, and has 55.7% chance of successfully recommending target dose levels. Since the dose level just below the lowest target dose level (1200 mg) has a DLT rate very close to 16%, there is a 44% chance of recommending the lower dose. The chance of recommending a toxic dose is very low in Scenario 3 (0.3%). The average number of patients required is approximately 18, with approximately 2 DLTs expected on average. In Scenario 4, with an even faster increase of DLT rate over doses, there is a 71.3% probability of recommending target dose levels, and the probability of recommending toxic doses is 11.7%. The average number of patients required is approximately 17 with 3 DLTs expected on average. In Scenario 5, when the starting dose is the only target dose, and the second dose level has a DLT rate relatively close to 33%, there is a 24.1% chance of claiming that the starting dose is the MTD, and an approximately 46.0% chance of claiming that all doses are toxic. Most of the patients (~60%) do not receive doses above the MTD dose. The average number of patients required is approximately 10 with fewer than 4 DLTs expected on average. In Scenario 6, where all doses are toxic, there is a 96.3% chance of successfully claiming that all doses are toxic. The average number of patients required is approximately 5, and fewer than 3 DLTs are expected on average.

[redacted]

The accuracy of the BLRM recommendation relies on the true DLT rate, thus the safety, clinical, PK, [redacted] data evaluations are combined to support the dose escalation. [redacted]

Table 13.a [redacted]

[redacted]

Table 13.b [redacted]

[redacted]

[redacted]

Table 13.c [redacted]

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and [redacted] before the phase 2a of this study is opened to enrollment. Approximately 5 dose levels are planned. For phase 1, the number of patients is planned to be approximately 21.

In phase 2a, up to a total of 18 patients will be treated to provide a preliminary estimate of the ORR in patients with r/r MM. All patients must show a clear evidence of PD with anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 13.d shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this relapse/refractory population.

Table 13.d 80% Confidence Interval Based on the Observed ORR

[redacted]

N=18 patients.
ORR=overall response rate.

[redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. 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 federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

[redacted]

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

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

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

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

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

15.3 Patient Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

[redacted]

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 in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's 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 to find 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 callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, 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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

[redacted]

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[redacted]

Appendix A Schedule of Events

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Informed consent (b)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
HBV, HCV, CMV, and HIV	X								
Height and weight (c)	X	X				X			
ECOG performance status	X	X				X			
ECG (d)	X	X				X			
		ECG measurements additionally on **Days 2, 3**, and **4** for Cycles 1 and 2 (see Section 9.4.12).							
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).								
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).								

[redacted]

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Dosing									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 injection (f)		X	X	X	X	X	X	X	X
Laboratory assessments									
Serum chemistry (g)	X	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X	X	X	X	X	X	X	X
Pregnancy test (j) (k)	X	X				X			
Response assessments for MM									
Serum M-protein	X	X				X			
Urine M-protein (l)	X	X				X			
Serum FLC assay (m)	X	X				X			
Immunofixation - serum and urine (n)	X	X				X			
Quantification of Ig	X	X				X			
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)	X								
Biological assessments									
Bone marrow aspiration (BMMCs) (p)	X					X			
Serum sample for TAK-079 PK (q)		X	X	X	X	X	X	X	X
		PK sampling additionally on **Days 2, 3**, and **4** for Cycles 1 and 2.							
[redacted]									
Serum sample for immunogenicity (ADA/titer) (s)		X				X			
[redacted]									
Serum sample for direct and indirect Coomb's test (s)		X				X			

Footnotes added on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 3 Through 6

	Treatment Phase (Every 2 Weeks)							
Study Period (Phases 1 and 2a)	**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Height and weight (c)	X		X		X		X	
ECOG performance status	X		X		X		X	
ECG (d)	X		X		X		X	
Physical examination	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).							
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).							
Dosing								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 injection (f)	X	X	X	X	X	X	X	X
Laboratory assessments								
Serum chemistry (g	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X	X	X	X	X	X	X
Pregnancy test (j) (k)	X		X		X		X	
Response assessments for MM								
Serum M-protein	X		X		X		X	
Urine M-protein (l)	X		X		X		X	
Serum FLC assay (m)	X		X		X		X	
Immunofixation - serum and urine (n)	X		X		X		X	
Quantification of Ig	X		X		X		X	
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)								
Biological assessments								
Bone marrow aspiration (BMMCs) (p)			X					
Serum sample for TAK-079 PK (q)	X	X	X	X	X	X	X	X

[redacted]

	Treatment Phase (Every 2 Weeks)							
Study Period (Phases 1 and 2a)	**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
[redacted]								
Serum sample for immunogenicity (ADA/titer) (s)	X		X		X		X	
[redacted]								
Serum sample for direct and indirect Coomb's test (s)	X		X		X		X	

Footnotes added on last page of SOE tables.

[redacted]

Treatment Period: Cycles 7 to Follow-up and Overall Survival Follow-up

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase		
					Survival	
Study Period (Phases 1 and 2a)	Cycle 7	Cycle 8	EOT/Early Termination	Follow-Up Visit	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	C7D1	C8D1	CXD1	--------	--------	--------
Window Allowed	±2 days	±2 days	±2 days	±7 days	± 7 days	± 7 days
Laboratory assessments						
Height and weight (c)	X	X	X	X		
ECOG performance status	X	X	X	X		
ECG (d)	X	X	X	X		
Physical examination	X	X	X	X		
Vital signs (e)	X	X	X	X		
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.					
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).					
	SAEs (includes pretreatment and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).					
Dosing						
Pre-injection medication	X	X	X			
TAK-079 injection (f)	X	X	X			
Laboratory assessments						
Serum chemistry (g)	X	X	X	X		
Hematology (h)	X	X	X	X		
Urinalysis (i)	X	X	X	X		
Pregnancy test (j) (k)	X	X	X	X		
Response assessments for MM						
Serum M-protein	X	X	X	X		
Urine M-protein (lj)	X	X	X	X		
Serum FLC assay (m)	X	X	X	X		
Immunofixation - serum and urine (n)	X	X	X	X		
Quantification of Ig	X	X	X	X		
Skeletal survey: WB X-ray; CT, low dose			X			

[redacted]

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase		
					Survival	
Study Period (Phases 1 and 2a)	**Cycle 7**	**Cycle 8**	**EOT/Early Termination**	**Follow-Up Visit**	**PFS Follow-Up Every 4 Weeks**	**OS Follow-Up Every 12 Weeks**
Cycle Day	**C7D1**	**C8D1**	**CXD1**	--------	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
CT, PET-CT, or MRI scan (o)						
Biological assessments						
Bone marrow aspiration (BMMCs) (p)	X					
Serum sample for TAK-079 PK (q)	X	X	X			
[redacted]						
Serum sample for immunogenicity (ADA/titer) (s)	X	X	X	X		
[redacted]						
Serum sample for direct and indirect Coombs Test (s)	X	X	X	X		
Disease status assessment (u)					X	
Survival (v)						X

Footnotes added on last page of SOE tables.

[redacted]

ADA=antidrug antibody; AE=adverse event; ALP=alkaline phosphatase ;ALT=alanine aminotransferase ; ANC=absolute neutrophil count ; AST=aspartate aminotransferase; BMA=bone marrow aspirate; BMMCs=bone marrow mononuclear cells; BUN=blood urea nitrogen; C=cycle; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; CXD1=Day 1 of additional treatment cycles (ie, after Cycle 8); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FLC=free light chain; GGT=gamma glutamyl transferase; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=Informed Consent Form; Ig=immunoglobulin; IR=injection reaction; LDH=lactate dehydrogenase; LPLV=last patient last visit; MM=multiple myeloma ; MRI=magnetic resonance imaging; OS=overall survival; PD=disease progression; PET-CT=positron emission tomography-computed tomography; PFS=progression-free survival; PK=pharmacokinetics; RBC=red blood cell(s);SAE=serious adverse event(s); SOE=Schedule of Events; V=visit; WB=whole body; WBC=white blood cell(s).

(a) The screening period is 21 days (ie, Days -21 to Day -1).
(b) Written informed consent must be obtained before performing any protocol-specific procedure.
(c) Height will be measured only at the Screening Visit. Weight will be measured at indicated visits.
(d) A single ECG will be collected at the screening visit. PK time-matched triplicate 12-lead ECGs will be collected during Cycles 1 and 2, as specified in Appendix B. Single 12-lead ECGs will be administered for all other designated visits (ie, after Cycle 2).
(e) Vital signs are measured prior to TAK-079 injection. Blood pressure will also be measured before starting each 2 mL injection, and at any time the patient complains of symptoms consistent with IR. Vital signs include temperature, pulse, respiratory rate, and blood pressure.
(f) Time and anatomical site should be recorded for each injection.
(g) Serum β_2 microglobulin levels will be measured at screening only. Refer to Section 9.4.13.1 for a list of clinical chemistry laboratory assessments.
(h) Refer to Section 9.4.13.1 for a list of hematology laboratory assessments.
(i) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. Refer to Section 9.4.13.1 for a list of urinalysis assessments.
(j) Pregnancy test (Refer to Section 9.4.8):

Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A serum pregnancy test will be performed during screening (within 10-14 days before start of study drug).
A serum pregnancy test is required within 24 hours before start of study drug.

(k) Pregnancy test (refer to Section 9.4.8):

On-treatment: a urine pregnancy test is required at designated study visits.
A urine pregnancy test is required at the follow-up visit in women of childbearing potential.
If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.

(l) Sampling required only if urine M-protein is measurable at Day 1 (visit 2).
(m) Blood sample obtained for the serum FLC assay to include quantification of kappa and lambda chains and ratio). To be analyzed locally.
(n) Will also be collected to confirm a CR.
(o) May be performed up to 21 days before first dose of TAK-079. Additional surveys (x-ray, CT, or MRI) may be performed at the investigator's discretion, eg, in case of bone pain. If disease is documented, then a repeat scan should be performed as required to document a response or PD.
(p) BMAs:

Samples will be taken during the screening phase, prior to treatment, and at the beginning of Cycles 2, 4, 7, and every 6 cycles (ie, 13, 19, 25, etc.) thereafter until

PD or intolerance. At screening, a standard BMA drawn prior to consent is acceptable provided this is collected within 5 weeks before the first dose.
For response assessment purposes, when a CR is suspected based on laboratory values, a BMA is required to confirm a CR. At the time of this procedure, 1 aspirate sample is analyzed locally for evaluation of disease, [redacted] It is also highly encouraged (optional) to perform an aspiration procedure in patients who achieve partial response as their best response. An aspirate for molecular analysis will also be collected at the time of disease relapse. This sample will be collected for PD confirmation or before starting new therapy and will be sent to the central laboratory for analysis.

(q) Blood samples for PK characterization will be collected at time points specified in Appendix B Pharmacokinetic Sampling Schedule. [redacted]

(s) Serum samples for immunogenicity assessment will be collected at baseline (before TAK-079 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. [redacted]

(u) Patients who discontinue treatment for reasons other than PD will continue to be followed every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

(v) Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

[redacted]

Appendix B Pharmacokinetic Sampling Schedule

Pharmacokinetic Assessments: Cycle 1

	Cycle 1										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before SC administration)	X	X							X	X	X
1 hour after SC administration (±15 min)		X									
2 hours after SC administration (±15 min)		X									
4 hours after SC administration (±30 min)	X	X									
8 hours after SC administration (±1 hour)	X	X									
24 hours after SC administration (±2 hours)			X	X							
48 hours after SC administration (±2 hours)					X	X					
72 hours after SC administration (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw. If multiple SC injections are required to administer the intended dose, post-dose PK and ECG assessments are to begin after administration of the final injection.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.

[redacted]

Pharmacokinetic Assessments: Cycle 2

	Cycle 2										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before SC administration)	X	X							X	X	X
1 hour after SC administration (±15 min)		X									
2 hours after SC administration (±15 min)		X									
4 hours after SC administration (±30 min)	X	X									
8 hours after SC administration (±1 hour)	X	X									
24 hours after SC administration (±2 hours)			X	X							
48 hours after SC administration (±2 hours)					X	X					
72 hours after SC administration (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw. If multiple SC injections are required to administer the intended dose, post-dose PK and ECG assessments are to begin after administration of the final injection.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.

[redacted]

Pharmacokinetic Assessments: Cycle 3 to Cycle 10

	Cycle 3 to Cycle 6		**Cycle 7 to Cycle 10**
	Day 1 (a)	**Day 15 (a)**	**Day 1 (a)**
Predose (within 1 hour before SC administration)	X	X	X

PK=pharmacokinetic; SC=subcutaneous.
If multiple SC injections are required in order to administer the intended dose, post-dose PK assessments are to begin after administration of the final injection.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.

[redacted]

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

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

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

[redacted]

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

[redacted]

Appendix E IMWG Criteria

IMWG Definition of MM

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically.
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of the normal range or >2.75 mmol/L (>11 mg/dL).
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL).
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡.
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%.
  - Involved: uninvolved serum free light chain ratio§ (FLC) ≥100.
  - >1 focal lesions on MRI studies.

* Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
† Measured or estimated by validated equations.
‡ If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, United Kingdom). The involved FLC must be ≥100 mg/L. Each focal lesion must be 5 mm or greater in size [15].

[redacted]

IMWG Uniform Criteria for Response

Category of Response	Response Criteria
sCR	Criteria for CR as defined below, with the addition of a normal FLC ratio, and an absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed (a).
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; 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; 2 consecutive assessments are needed (b).
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 >4 colors).
Molecular CR	CR as defined, plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; 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; 2 consecutive assessments are needed (c).
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed (a) no known evidence of progressive or new bone lesions if radiographic studies were performed.
Minimal response (MR) (b)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the 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).

[redacted]

Category of Response	Response Criteria
SD (c)	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

Source: Rajkumar SV et al, 2011 and Palumbo A et al, 2014 [9,10].
CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.
(a) Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
(b) For relapse-refractory myeloma only.
(c) These categories do not contribute to the ORR.

Before the institution of any new therapy, sCR, CR, and VGPR 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.

PD is defined as an increase of ≥25% from lowest response value in any of the following:

a) Serum M-protein (absolute increase must be ≥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

b) Urine M-protein (absolute increase must be ≥200 mg/24 hour), and/or

c) Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL).

d) Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%).

Or

a) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

b) Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Clarifications to IMWG criteria for coding PD: 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 tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

[redacted]

Appendix F ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM et al, 1982 [11].
ECOG=Eastern Cooperative Oncology Group.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	16-Oct-2017 18:41 UTC
[redacted]	Biostatistics Approval	16-Oct-2017 18:43 UTC

PROTOCOL

A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Study Number:	TAK-079-1501
IND Number:	136,414 **EudraCT Number:** Not applicable
Compound:	TAK-079
Date:	08 December 2017 **Amendment Number:** 01

Amendment History:

Date	Amendment Number	Region
12 October 2017	Initial Protocol	Global
08 December 2017	01	Global

[redacted]

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.0 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
Serious adverse event and pregnancy reporting	See Section 10.0

[redacted]

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 on Harmonisation E6 Good Clinical Practice: 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]
Dec 9, 2017

[redacted] Date
[redacted], MD, PhD
Global Medical Affairs
Distinguished Research Fellow Oncology

[redacted] Date
[redacted], PhD
Global Statistics

[redacted] Date
[redacted], PharmD, PhD
[redacted]
Quantitative Clinical Pharmacology

[redacted]

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

[redacted]

1.3 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

This document describes the changes in reference to the protocol incorporating Amendment 01. The primary reason for this amendment is to incorporate changes requested by the United States Food and Drug Administration during review of the original protocol.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only. For specific descriptions of text changes and where the changes are located, see Appendix G.

Changes in Amendment 01

1. The number of TAK-079 dose levels planned for phase 1 was changed to 6. The 400 mg dose level was removed, and the 300 and 600 mg dose levels were added.
2. Planned enrollment was increased to 24 patients for the phase 1 portion (42 patients overall).
3. Eligibility based on laboratory criteria for determining adequate organ function was clarified for patients with Gilbert's syndrome.
4. Inclusion criteria were modified to revise requirements for prior myeloma therapies and assessment of CD38 expression.

[redacted]

6. Exclusion criteria were modified to exclude patients with a higher risk of respiratory complications (chronic obstructive pulmonary disease with forced expiratory volume <80%).
7. An exclusion criterion was added to exclude patients with positive Coombs tests at screening.
8. The description of investigational agents was revised.
9. The definition of dose-limiting toxicities (DLTs) was modified to exclude relationship in determining a DLT, to include Grade 4 laboratory abnormalities clearly unrelated to the underlying disease as DLTs, and to note that events clearly due to extraneous causes will not be considered DLTs.
10. The dose escalation schema was changed to a 3+3 design from a Bayesian logistic regression model.
11. Dose modification recommendations in the event of Grades 3 and 4 adverse events were modified.
12. Instructions for handling infusion reactions were added to provide further instruction according to reaction grade.
13. Methods for disease response imaging were clarified, including addition of a skeletal survey starting at Cycle 6.
14. Text was added to the safety analysis methods regarding Grade 4 or higher nonhematologic toxicities occurring in the Phase 2a portion of the study.

[redacted]

[redacted]

16. A serum sample for immunogenicity assessment was added on Cycle 1 Day 15.
17. The pharmacokinetic sampling schedule was revised to reflect sample collection times relative to the first injection, rather than the final injection, when multiple injections are required to administer the intended dose. [redacted]

[redacted]

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[redacted]

LIST OF IN-TEXT TABLES

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LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

[redacted]

2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-079	
Title of Protocol: A Phase 1/2a, Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma		
Study Number: TAK-079-1501	**Phase:** 1/2a	

Study Design:

This is a multicenter, open-label, dose-escalation, single-arm, phase 1/2a study designed to determine the safety and tolerability of TAK-079 monotherapy in patients with relapsed or refractory (r/r) multiple myeloma (MM), and to provide a preliminary assessment of its activity against r/r MM.

Once enrolled into the study, patients will receive TAK-079 via subcutaneous (SC) administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until disease progression (PD). Patients will receive ongoing treatment with TAK-079 until PD, unacceptable toxicities, or withdrawal due to other reasons.

The phase 1 portion of the study will evaluate administration of TAK-079 for dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) for further assessment in phase 2a. A recommended dose below the MTD may be identified based on the review of safety, pharmacokinetic (PK), [redacted], and clinical data from the phase 1 portion of the study.

The safety and tolerability of TAK-079 will be assessed by recording and analyzing treatment-emergent adverse events (TEAEs), dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology, urinalysis, electrocardiograms, and concomitant medications. In phase 1, approximately 6 doses of TAK-079 will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. In the phase 2a portion of this study, Grade 4 or higher nonhematologic toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients thereafter.

It is expected that approximately 42 patients will be enrolled in the study. The estimated duration of the study is approximately 48 months (ie, 4 years).

Primary Objectives:

Phase 1

To determine the safety, tolerability, and the MTD/RP2D of TAK-079 monotherapy in patients with r/r MM.

Phase 2a

To provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with r/r MM.

Secondary Objectives:

Phase 1

- To investigate a potential MTD/RP2D of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

Phase 2a

- To further evaluate safety at the MTD/ RP2D.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

[redacted]

Exploratory Objectives:
Phase 1 and 2a

[redacted]

Subject Population: Subjects aged 18 years or older, with r/r MM, and Eastern Cooperative Group (ECOG) performance status of ≤2

Number of Subjects:	**Number of Sites:**
Phase 1: approximately 24 patients. Phase 2a: approximately 18 patients.	Phase 1: approximately 4 investigational centers. Phase 2a: approximately 6 investigational centers.
Dose Level(s): TAK-079 injections will be escalated as follows: 45 mg, 135 mg, 300 mg, 600 mg, 1200 mg, and 1800 mg in phase 1. After patients have received premedication treatment, doses will be administered with syringes as SC injections up to a maximum of 200 mg TAK-079 in 2 mL per injection, injected every 30 minutes until the full scheduled dose has been administered. Each dose will be administered as once weekly for 8 weeks (8 doses), then once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks until PD or unacceptable toxicities occur. For phase 2a, in the absence of DLT, the dose will be selected based upon review of the available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study. Premedication will be mandatory in phase 1. The decision to premedicate in phase 2a will be determined based on data from phase 1.	**Route of Administration:** Route of administration will be SC.
Duration of Treatment: TAK-079 will be administered until the patient experiences PD, unacceptable toxicities, or withdrawal due to other reasons.	**Period of Evaluation:** 21 days screening, ongoing treatment to PD. Patients who discontinue treatment for reasons other than PD will continue to be followed for progression-free survival (PFS) every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after the last patient has received their last dose (LPLD). Overall survival (OS): Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

[redacted]

Main Criteria for Inclusion:

Male and female patients, aged ≥18 years, with ECOG performance status of ≤2, requiring additional therapy as determined by the investigator. Patients must have received the final dose of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079: 120 days for antibody therapy (including anti-CD38), 90 days for autologous transplantation, and 30 days for chemotherapy, corticosteroid therapy (up to systemic equivalent of 10 mg daily prednisone allowed), radiation therapy, and major surgery. Patients must have adequate organ function as determined by the following laboratory values: absolute neutrophil count $\geq 1.0 \times 10^9$/L; platelets $\geq 75{,}000/mm^3$ ($\geq 75 \times 10^9$/L); hemoglobin ≥7.5 g/dL; creatinine clearance ≥30 mL/min (Cockcroft-Gault formula); total bilirubin ≤1.5 times the upper limit of the normal range (ULN); and alanine aminotransferase/aspartate aminotransferase ≤2.5×ULN. Patients must have documented r/r MM per the International Myeloma Working Group (IMWG) criteria, with measurable disease defined as one of the following: serum M-protein ≥500 mg/dL (≥0.5 g/L) and urine M-protein ≥200 mg/24 hours. Patients without measurable M-protein in serum protein electrophoresis or urine protein electrophoresis must have a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal. Patients must have evidence of r/r MM as defined by the IMWG criteria, previously received at least 3 lines of myeloma therapy including a PI, IMid, alkylating agent, and steroids. Previous exposure to anti-CD38 as single agent or in combination is allowed but is not mandatory. Patients must be refractory to or intolerant of at least 1 PI and 1 IMid. Patients who received a combination of PI and IMid in a unique treatment schedule can be included in the study after at least 2 lines of prior myeloma therapy. Prior treatment with an anti-CD38 monoclonal antibody (mAb) is allowed; however, CD38 expression must be significantly expressed on target cells for this mechanism of action to be effective. In the phase 2a portion of the study, patients must have been refractory to an anti-CD38 mAb therapy at any time during treatment.

Main Criteria for Exclusion:

Sensory or motor neuropathy of Grade ≥3, based on the National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) or not recovered from adverse reactions to prior myeloma treatments/procedures to NCI CTCAE Grade ≤1 or baseline; allogeneic stem cell transplant; congestive heart failure (New York Heart Association) Grade ≥II, cardiac myopathy, active ischemia, clinically significant arrhythmia, history of acute myocardial infarction within 5 months before enrollment, clinically significant uncontrolled hypertension, or any other uncontrolled cardiac condition or concurrent illness that would preclude study conduct and assessment; QT interval corrected by the Fridericia method >480 msec (Grade ≥2); history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-079 formulation (including patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction); history of myelodysplastic syndrome or another malignancy other than MM; clinical signs of central nervous system involvement of MM; or active chronic hepatitis B or C infection, active HIV infection, or active cytomegalovirus infection. Also excluded are patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance; smoldering myeloma; solitary plasmacytoma; amyloidosis; Waldenström macroglobulinemia or immunoglobulin M myeloma, and patients with positive Coombs tests at screening.

Endpoints (in order of importance):

Primary:

Phase 1

- The number of patients with TEAEs overall and per dose level.
  - Patients with DLTs at each dose level.
  - Patients with Grade ≥3 TEAEs.
  - Patients with SAEs.
  - Patients who discontinue because of TEAEs.
  - Patients with dose modifications (delays, interruptions, dose reductions).
    - Clinically significant laboratory values as determined by the investigator.
    - Clinically significant vital sign measurements as determined by the investigator.

Phase 2a

- Overall response rate (ORR), defined as the proportion of patients who achieved a partial response ([PR]; 50% tumor reduction) or better during study as defined by IMWG Uniform Response Criteria.

[redacted]

Secondary:

Phase 1

- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079 will be assessed in patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria.
  - Proportion of patients who achieved minimal response (MR), defined as 25% tumor reduction.
- Anti–TAK-079 antibody incidence and characteristics.

Phase 2a

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction, will be evaluated.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the time from the date of the first dose to the date of the death due to any cause.
- Time to response, defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

Exploratory:

[redacted]

Statistical Considerations:

The MTD/RP2D will be estimated by a 3+3 dose escalation design using data collected in the dose-escalation phase of the study. After review of the available safety, efficacy, PK, [redacted] data, additional cohorts may be expanded by enrolling additional patients to obtain a more comprehensive assessment of disease response and to further inform selection of the R2PD.

Adverse events (AEs) will be summarized by treatment group and overall. Categorical variables such as ORR will be tabulated by treatment group and overall. Time to event variables such as DOR and PFS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided.

PK parameters will be summarized as appropriate.

[redacted]

Sample Size Justification:

Phase 1 of the study will follow a 3+3 dose escalation schema.

The selection of the next recommended dose will be determined based on safety, clinical, PK, [redacted] data. Dose-escalation cohorts may be expanded to include additional patients to obtain a more comprehensive assessment of disease response before the phase 2a portion of this study is opened to enrollment. Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 24.

In phase 2a, approximately 18 additional patients will be treated to provide a preliminary estimate of the ORR in patients with r/r MM. All patients with MM must show clear evidence of PD with anti-CD38 therapy.

Phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

No prospective calculations of statistical power have been made; however, the following table shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this r/r population.

[redacted]

[redacted]

3.0 STUDY REFERENCE INFORMATION

Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (Appendix C). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

Principal Investigator

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

[redacted]

3.1 List of Abbreviations

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BMA	bone marrow aspirate
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form (refers to any media used to collect study data [ie, paper or electronic])
EOI	end of infusion
EOT	end of treatment
FDA	United States Food and Drug Administration
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
[redacted]	[redacted]

[redacted]

Abbreviation	Term
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IR	injection reaction
IRB	institutional review board
IV	intravenous(ly)
LPLD	last patient, last dose
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAB	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PB	plasmablast
PD	progressive disease; disease progression
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS syndrome	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
PR	partial response
QTc	QT interval corrected for heart rate
RBC	red blood cell(s)
r/r	relapsed or refractory
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SCRS	severe cytokine release syndrome
SOE	Schedule of Events
SPEP	serum protein electrophoresis

Abbreviation	Term
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration
[redacted]	[redacted]
TTR	time to response
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WOCBP	women of child-bearing potential

4.0 INTRODUCTION

4.1 Background

TAK-079 is a fully human antibody of the immunoglobulin G1 (IgG1) subclass, which targets CD38 expressing cells for destruction through multiple mechanisms of action (complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity). TAK-079 treatment results in a rapid depletion of CD38+ leukocytes in the peripheral blood, as observed in nonhuman primate studies and in humans. A number of hematologic tumors express CD38, including multiple myeloma (MM), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and B-cell non-Hodgkin lymphoma.

MM is a plasma cell-derived malignancy that accounts for approximately 1% of all cancers [1]. It is characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency. The 5-year survival rate of patients with MM is approximately 45% [1]. MM persists as a mostly incurable disease due to its highly complex and diverse cytogenetic and molecular abnormalities [2]. There has been improvement in the outcome for patients with MM in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory drugs (IMiDs) like lenalidomide, but patients who become refractory or are ineligible to receive PIs and IMiDs have a dismal prognosis [3]. In November 2015, the United States Food and Drug Administration (FDA) approved the CD38 antibody daratumumab (DARZALEX; Janssen) for the treatment of MM [4]. Daratumumab was studied in patients who had received at least 3 prior lines of therapy including a PI and an IMiD, or who were double-refractory to these agents. An overall response rate (ORR) of 29% was documented, including a 3% rate of complete response (CR)/stringent complete response (sCR). The main toxicity associated with daratumumab was infusion reactions, which were severe in some patients. Other common adverse reactions were fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection [5]. Notably, not all patients respond and many patients eventually develop progressive disease on daratumumab monotherapy [6].

4.2 Findings From Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies are provided below. More detailed information is provided in the TAK-079 Investigator's Brochure (IB).

[redacted]

[redacted] Systemic exposures in the 13-week toxicity studies were considered adequate for assessment despite the formation of antidrug antibodies (ADA) observed more frequently at the lower doses, which negatively affected exposures likely via increased clearance. Assessments of local tolerance via either IV or subcutaneous (SC) dosing routes indicated no significant local injection site liabilities. Collectively, these data support the continued use of TAK-079 in humans.

4.2.1 [redacted]

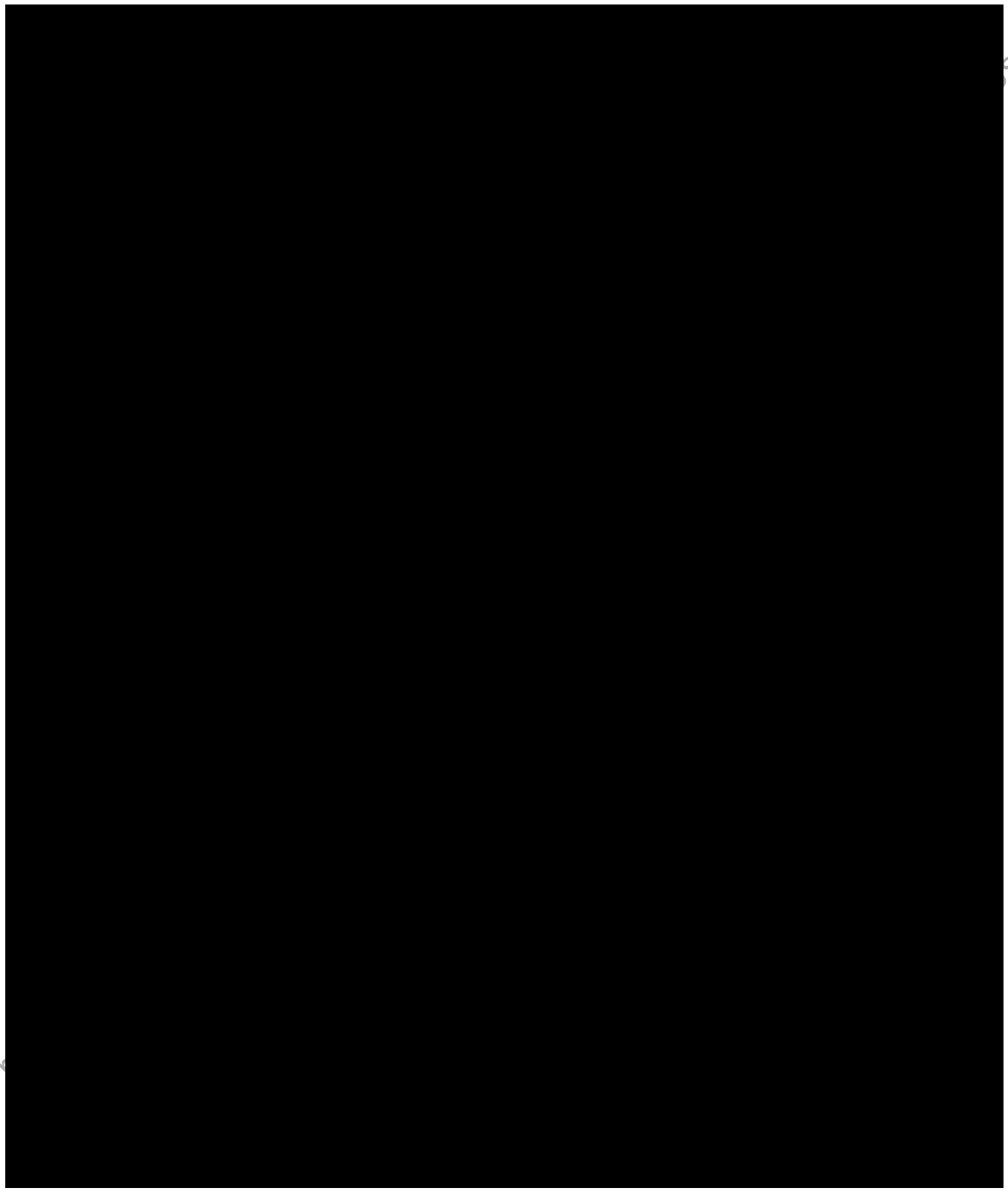
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



4.3 Known and Potential Benefits and Risks to Patients with TAK-079

TAK-079 was administered only in healthy human subjects in the first-in-human (FIH) study (TAK-079_1001). Only mild or moderate AEs were observed in the FIH study in healthy subjects. Therefore, clinical benefits and risks have not been assessed in the disease setting.

A summary of findings is discussed in Section 4.3.1. See details for precautions and restrictions in Section 8.7. Additional information regarding potential risks from treatment is provided in the TAK-079 IB.

4.3.1 Risks

Based on the mechanism of action of TAK-079, potential risks may include infusion or injection reactions, hematological effects, and serious infections.

4.3.1.1 Infusion and Injection Reactions

Infusion reactions are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents aimed at treating hematologic malignancies. Infusion reactions are less frequently associated with SC injection of these therapies. The 'true' clinical hypersensitivity reactions, antibody-mediated occur after repeat exposure. Symptoms of hypersensitivity range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Non-anaphylactic clinical hypersensitivity occurs within the first hour; however delayed responses were reported. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, bronchospasm, respiratory distress, and shock.

There are limited nonclinical and clinical data to date for TAK-079 (Section 4.2.1). Significant local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. However, patients in clinical trials receiving TAK-079 will be carefully monitored for signs and symptoms of IR, with appropriate management of these events. Depending on the severity of the reaction, management may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

See additional details for managing IRs in Section 8.8.1.

4.3.1.2 Cytokine Release Syndrome

CRS represents an important infusion reaction often associated with the use of monoclonal antibodies used in anti-inflammatory and antitumor therapies. CRS may occur in early phases of therapy, and often after the first infusion of the drug due to 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 also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting. Anaphylactoid reactions are characterized by chills, rigors, hypotension or hypertension, tachycardia, and/or loss of consciousness.

[redacted]

In the FIH study conducted in healthy human subjects, rarely-observed symptoms consistent with CRS of mild severity were reported particularly at higher doses, and they did not require dose adjustment or interruption. Potential occurrence of events associated with CRS will be carefully monitored in patients receiving TAK-079 and managed according to institutional guidelines.

[redacted]

4.3.1.3 Severe Cytokine Release Syndrome

Severe cytokine release syndrome (SCRS) is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumor lysis syndrome such as hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated lactate dehydrogenase, and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

4.3.1.4 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the NOAEL. Subjects in clinical studies of TAK-079 should be monitored closely, including testing of hematology parameters.

The important potential risk of these hematologic changes will be monitored throughout this clinical study, as described in Section 9.4.13 and Appendix A.

4.3.1.5 Serious Infections

In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

Subjects will be monitored for any signs and symptoms of the important potential risk of serious infections throughout this clinical study (see Section 8.8.3).

4.3.1.6 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 monoclonal antibody (mAb), the risk of drug-drug interactions is low.

4.3.1.7 ADA Interactions

ADA responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Strong positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeat-dose toxicity studies and at lower doses.

In the single-dose healthy subject study (TAK-079_101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these,

1 subject was treated in the 0.06 mg IV cohort and the remaining 4 subjects were treated with either 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity.

4.3.1.8 Pregnancy and Lactation

TAK-079 has not been administered to women who are pregnant or lactating. Dedicated fertility and embryo-fetal development toxicology studies have not been conducted with TAK-079. However, there were no TAK-079–related changes in organ weights or microscopic findings noted in the male and female reproductive tract of monkeys following administration for up to 13 weeks. Women of child bearing potential (WOCBP) may be enrolled in clinical trials with appropriate precautions to prevent pregnancy (additional details in Section 8.7).

At this stage of development TAK-079 should not be administered to women who are pregnant or breastfeeding.

4.3.1.9 Overdose

TAK-079 has been administered only to healthy subjects in the FIH study. To date, there is no experience with overdose. If an overdose does occur, close monitoring and supportive treatment as required are recommended.

4.3.2 Overall Benefit and Risk Assessment for This Study

The overall clinical benefits and risks of TAK-079 have not been determined.

Based on the mechanism of action of TAK-079, nonclinical data to date, as well as some exposure in healthy human subjects, risks of TAK-079 include but are not limited to IRs, CRS, hypersensitivity reactions, changes in hematologic parameters, and serious infections. Patients will be monitored closely for these risks in this clinical study.

4.4 Rationale for the Proposed Study

Although multiple therapies are available for patients with MM, this disease remains incurable; thus, significant unmet medical need exists for this patient population. Frequent relapses highlight a need for new therapies for patients in whom prior treatments have failed.

TAK-079 binds a partially distinct epitope of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab. Unlike daratumumab, TAK-079 does not bind to RBCs and platelets. Therefore, TAK-079 may possess higher tumoricidal activity than daratumumab because cytolytic effector activity is focused on CD38+ leukocytes/tumors and is not misdirected to RBCs and platelets. Consequently, TAK-079 may demonstrate higher potency (ie, activity at lower doses and exposures) and activity in daratumumab-refractory tumors (ie, tumors expressing lower levels of CD38) and thus be more efficient at eliminating tumors.

In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed.

In summary, it is feasible to investigate administration of TAK-079 in patients with relapsed or refractory (r/r) MM.

4.4.1 Rationale for the Starting Dose of TAK-079

In the FIH study (TAK-079_101), TAK-079 was well tolerated after SC administration of single-doses ranging from 0.03 to 0.6 mg/kg.

To avoid unnecessary exposure of patients to sub-therapeutic doses while preserving safety, the starting dose for this study in patients with r/r MM will be 45 mg, the fixed-dose equivalent of 0.6 mg/kg (assuming a body weight of 75 kg), which was the highest SC dose administered in Study TAK-079_101. The 0.6 mg/kg dose was well tolerated in healthy human subjects in Study TAK-079_101 and demonstrated depletion of peripheral blood PBs, a surrogate for tumor cells.

TAK-079 is a mAb targeting CD38, which is a cell surface molecule that is constitutively expressed on plasma cells, PBs, and NK cells, and is induced on activated T cells and B cells [7]. Therefore, the anticipated elimination routes for TAK-079 are via proteolytic catabolism and intracellular degradation after binding to its target. Both of these clearance mechanisms are not thought to be significantly influenced by body weight. Additionally, the distribution volume of mAbs is generally limited to the volume of the blood and extracellular fluids, such that body composition is a less important determinant of distribution volume as compared with small molecule drugs [8]. For these reasons, body weight is not expected to have a clinically significant effect on the disposition of TAK-079, thereby supporting the investigation of fixed-dose administration.

The 45 mg starting dose of TAK-079 will be tested in 3 patients with r/r MM to assess the safety and tolerability of TAK-079 after multiple dose administration. TAK-079 will be administered using the same dosing schedule as the anti-CD38 antibody, daratumumab, which is approved for the treatment of patients with MM [5]. Specifically, TAK-079 will be administered once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), then once every 4 weeks until the patient experiences disease progression (PD), unacceptable toxicities, or withdrawal due to other reasons. The subsequent planned dose levels are 135, 300, 600, 1200, and 1800 mg.

Escalation to a subsequent cohort may take place after the treatment in the first cycle of the previous (sequential) cohort has completed.

Additional details for dose escalation are provided in Section 8.3.

[redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Phase 1 Primary Objective

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy in patients with r/r MM.

5.1.2 Phase 1 Secondary Objectives

The secondary objectives are:

- To investigate a potential maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

5.1.3 Phase 2a Primary Objective

The primary objective of the phase 2a portion of the study is to provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with r/r MM.

5.1.4 Phase 2a Secondary Objectives

The secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

5.1.5 Phase 1 and Phase 2a Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Phase 1 Primary Endpoints

The primary endpoints for phase 1 are:

- The number of patients with TEAEs overall and per dose level.
  - Patients with dose-limiting toxicities (DLTs) at each dose level.
  - Patients with Grade ≥3 TEAEs.
  - Patients with SAEs.
  - Patients who discontinue because of TEAEs.
  - Patients with dose modifications (delays, interruptions, dose reductions).
  - Clinically significant laboratory values, as determined by the investigator.
  - Clinically significant vital sign measurements, as determined by the investigator.

5.2.2 Phase 2a Primary Endpoint

The primary endpoint for phase 2a is:

- ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria [9,10].

5.2.3 Phase 1 Secondary Endpoints

The secondary endpoints for phase 1 are:

- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079 will be assessed for patients with MM:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria ([9,10]; Appendix E).
  - Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction ([9,10]; Appendix E).
- Anti–TAK-079 antibody incidence and characteristics.

[redacted]

5.2.4 Phase 2a Secondary Endpoints

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause ([9, 10], Appendix E).
- Overall survival (OS), defined as the time from the date of first dose to the date of death due to any cause.
- Time to response (TTR), defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

5.2.5 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients with r/r MM, and to provide a preliminary assessment of its activity against MM.

The phase 1 portion of the study will evaluate administration of TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs, dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, and review of concomitant medications.

The preliminary efficacy of TAK-079 will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [9,10]). In addition, the efficacy of TAK-079 will be assessed by measuring PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the study, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or withdrawal due to other reasons.

Phase 1 will consist of the following phases/periods: Screening, Treatment, and Follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing): Once-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.
- Follow-up Period (follow-up visit): Patients who discontinue for PD will be followed for 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after the last patient has received their last dose (last patient, last dose [LPLD]). All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

In phase 1, approximately 6 doses will be evaluated in ascending cohorts of 3-6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

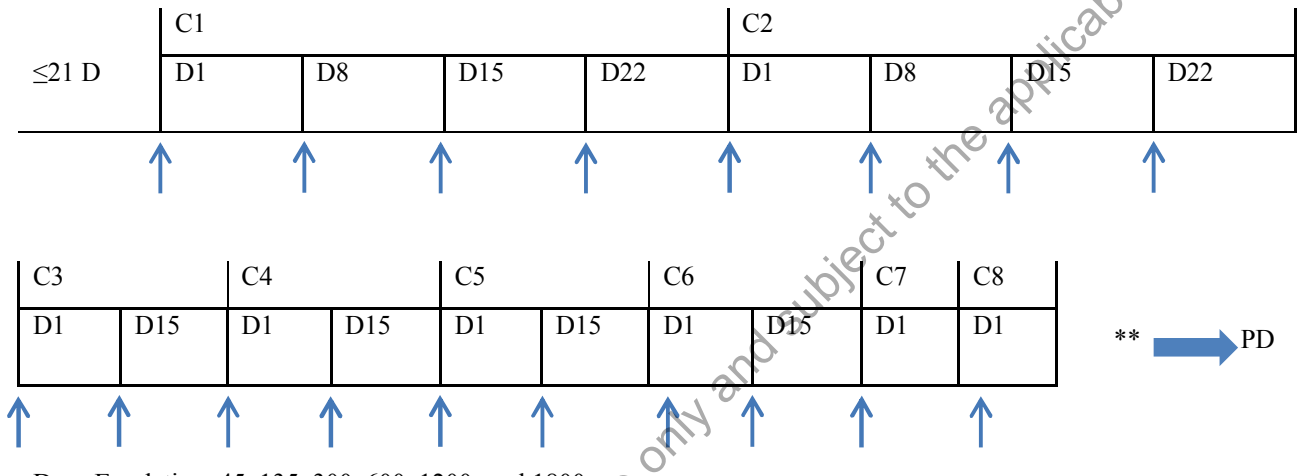
[redacted]

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined. The estimated duration of the study is approximately 48 months (4 years; Section 6.3).

Study procedures and assessments, with their time points, are shown in Appendix A. The study schematic diagram is shown in Figure 6.a.

Figure 6.a Overall Study Schematic Diagram

Treatment Cycle



Dose Escalation: 45, 135, 300, 600, 1200, and 1800 mg.
Cohorts in phase 1 may be expanded to further inform selection of the RP2D.
The RP2D determined in phase 1 will be further assessed in approximately 18 patients in phase 2a.
** → = dosing every 28 days until disease progression.
↑ = TAK-079 dose; C=Cycle; D=Day; R2PD=recommended phase 2 dose.

6.2 Number of Patients

For phase 1, approximately 24 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 18 patients are planned. Details on the definition of evaluable patients and sample size are given in Section 13.1.

The study is planned to be conducted in the United States in approximately 4 investigational centers for phase 1 and in a total of 6 investigational centers for phase 2a.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-079 until they experience PD as defined by IMWG for patients with MM ([9,10]; Appendix E), unacceptable toxicity, withdrawal of consent, death, termination of the study by the sponsor, until any other discontinuation criterion is met, or until 12 months after LPLD (additional participation details are provided in Sections 6.1, 8.4.3, 9.6, and 9.7).

Patients will be evaluated 30±7 days after the last dose of TAK-079 (follow-up visit) or before initiating subsequent systemic anticancer therapy, for detection of any delayed TEAEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final data cutoff for the clinical study report will be conducted 12 months after all patients have been discontinued from treatment or transferred to a long-term safety study, a single-patient investigational new drug application, or a similar program (Table 6.a).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

[redacted]

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint		Definition	Maximum Time Frame From Final Clinical Study Report
Phase 1			
Primary:	Number of patients with TEAEs overall and per dose level: number of patients with TEAEs overall and per dose level; patients with DLTs at each dose level; patients with Grade ≥3 TEAEs; patients with SAEs; patients who discontinue because of TEAEs; patients with dose modifications (delays interruptions, dose reductions), clinically significant laboratory and vital sign values, as determined by the investigator	Includes assessments for patients with DLTs, Grade ≥3 TEAEs, SAEs, discontinuations because of TEAEs, dose modifications, and clinically significant laboratory values and vital signs.	1 year
Secondary:	Summary statistics for PK parameters: C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: MR	Proportion of patients who achieved a minimal response, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary:	Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year

[redacted]

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

Endpoint	Definition	Maximum Time Frame From Final Clinical Study Report
Phase 2a		
Primary: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary: DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, clinically significant laboratory values, and vital signs.	Includes assessments for patients with DLTs and other TEAEs, dose modifications, treatment discontinuations, clinically significant laboratory values, and vital signs.	1 year
Secondary: Summary statistics for PK parameters of C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).See Section 13.1.4.	1 year
Secondary: Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year
Secondary: MR	Proportion of patients who achieved MR, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary: DOR	Time from the date of the first documentation of response to the date of the first documented PD. See Section 13.1.3.	1 year
Secondary: PFS	Time from the date of the first dose until the earliest date of PD, or the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: OS	Defined as the time from the date of first dose to the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: TTR	Time from the date of the first dose to the date of the first documentation of response (PR or better). See Section 13.1.3.	1 year

DLT=dose-limiting toxicity; DOR=duration of response; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTR=time to response.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 48 months (4 years).

[redacted]

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. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 [11].
3. Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079 (Table 7.a):

Table 7.a Required Washout Periods for Previous Treatments or Procedures Prior to Administration of TAK-079

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	30 days
Antibody therapy (including anti-CD38)	120 days
Corticosteroid therapy (a)	30 days
Autologous transplantation	90 days
Radiation therapy	30 days
Major surgery	30 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.

4. Patient has adequate organ function as determined by the following laboratory values (Table 7.b):

Table 7.b Laboratory Criteria for Determining Adequate Organ Function for Study TAK-079-1501 Eligibility

Laboratory Parameter	Acceptable Laboratory Criteria
Absolute neutrophil count (a)	≥1000/mm^3 (≥1.0×10^9/L); ≥750/mm^3 (≥0.75×10^9/L) maybe acceptable for patients with >50% of plasma cells in bone marrow after discussion with sponsor
Platelets (a)	≥75,000/mm^3 (≥75×10^9/L); a 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
Hemoglobin	≥7.5 g/dL (it is not permissible to transfuse a subject to reach this level)
Creatinine clearance	≥30 mL/min (Cockcroft-Gault formula)
Total serum bilirubin	≤1.5×ULN; except for patients with Gilbert's syndrome in whom direct bilirubin should be <2.0×ULN
Liver transaminases (ALT/AST)	≤2.5×ULN

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.
(a) Without ongoing growth factor or transfusion support for at least 1 week before Day 1.

5. Female patients who:
   - Are WOCBP must not be pregnant or lactating.
   - 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 at least 30 days or 5 half-lives after the last dose of study drug, whichever time period is longest, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
6. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
8. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.
9. Requires additional therapy, as determined by the investigator.
10. Documentation of r/r MM as defined by the IMWG criteria (Appendix E; [9,10]).
11. For patients with MM, measurable disease defined as one of the following:
    - Serum M-protein ≥500 mg/dL (≥5 g/L).
    - Urine M-protein ≥200 mg/24 hours.

[redacted]

- 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.

12. Prior therapy should meet all of the following criteria:
    - Patient should be previously treated with at least a PI, an IMid, an alkylating agent, and a steroid.
    - Patient should be refractory or intolerant to at least 1 PI and at least 1 IMid.
    - Patient should either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMid.
    - Previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required.
13. Patients must express CD38 on target cells with a mean fluorescence intensity ≥1000 units on ≥90% of plasma cells as determined by multicolor flow cytometry.
14. In the phase 2a portion of the study, patients with MM must also have been refractory to at least 1 anti-CD38 mAb therapy at any time during treatment.

NOTE:

- Refractory is defined as at least a 25% increase in M-protein or PD during treatment or within 60 days after cessation of treatment.
- A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of PD, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease [9].

7.2 Exclusion Criteria

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

1. Sensory or motor neuropathy of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 [12].
2. Patients who have received allogeneic stem cell transplant.
3. Patients who have received anti-CD38 antibody therapy and do not fulfill a 120-day washout period before receiving TAK-079.
4. Not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE Grade ≤1 or baseline.

5. Congestive heart failure (New York Heart Association) Grade ≥II; cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.
6. History of acute myocardial infarction within 5 months before enrollment or ECG abnormalities during the screening period that are deemed medically relevant by the investigator.
7. QT interval corrected by the Fridericia method >480 msec (Grade ≥2).
8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume <80%, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.
9. History of stroke or intracranial hemorrhage within 12 months of randomization; patients requiring anticoagulation therapy for any indication should be discussed with the medical monitor before screening.
10. Active autoimmune disease including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or any chronic condition requiring a higher corticosteroid systemic equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped 30 days prior to randomization; exceptions may be made for corticosteroids prescribed specifically for management of MM symptoms after discussion with the medical monitor.
11. History of myelodysplastic syndrome or another malignancy other than MM, except for the following: any malignancy that has been in complete remission for 3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, or asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year before the start of study therapy.
12. Clinical signs of CNS involvement of MM.
13. Female patients who are pregnant with a positive serum pregnancy test or lactating during the screening period, or a positive urine pregnancy test on Day 1 before the first dose of study drug, if applicable.
14. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, active HIV, or cytomegalovirus (CMV) infection.

[redacted]

16. History of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation. This includes patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction.
17. The patient is currently participating in another antimyeloma or antileukemia clinical study, or has participated in another investigational clinical trial within the past 4 weeks prior to randomization.
18. Patients who are not able and/or willing to comply with the study requirements, rules, and procedures.
19. POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, or IgM myeloma.
20. Patients with positive Coombs tests at screening.

[redacted]

8.0 STUDY DRUG

8.1 Study Drug Administration

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

8.1.1 Premedication

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor) is optional for Cycle 1 Day 1.

NOTE: Patients with a higher risk of respiratory complications (eg, patients with a history of COPD and patients with asthma) will be treated with postinjection medication consisting of the following:

- An antihistamine (diphenhydramine or equivalent) on the first and second days after all injections,
- A short-acting β_2 adrenergic receptor agonist, such as salbutamol (albuterol) aerosol, and
- Control medications for lung disease (eg, inhaled corticosteroids with or without long-acting β_2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol with or without inhaled corticosteroids for patients with COPD).

Premedication will be mandatory in phase 1. The decision to premedicate in phase 2a will be determined based on data from phase 1.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

8.1.2 TAK-079 Formulation and Administration

The strength of the TAK-079 drug product for SC use in the current study (TAK-079-1501) is 100 mg TAK-079 in 1 mL (100 mg/mL). The drug product is supplied in clear borosilicate glass vials (see additional details in Section 8.10).

After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL), injected every 30 minutes until the full scheduled dose has been administered.

Patients may receive low-dose methylprednisolone (≤ 20 mg) for the prevention of delayed injection related reaction, as clinically indicated.

Refer to the Pharmacy Manual for detailed instructions regarding preparation of each dose.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [12]. These criteria are provided in the Study Manual. DLTs will be defined as any of the following events regardless of relationship, except those events that are clearly due to extraneous causes.

- Grade 4 laboratory abnormalities, except those events that are clearly due to extraneous causes, will be defined as a DLT.
- Nonhematologic TEAEs of NCI CTCAE Grade ≥3, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - Grade 3 nausea/vomiting that can be managed subsequently with antiemetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 72 hours.
  - Grade 3 elevation of ALT or AST that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms.
- Hematologic TEAEs of NCI CTCAE Grade ≥4, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis, except those events that are clearly due to extraneous causes (eg, negative direct Coombs test), will be included in the definition of DLT.
  - Grade 3 low platelet or higher count with clinically meaningful bleeding will be included in the definition of DLT.
- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a DLT.

For the purpose of dose escalation, DLTs are those events meeting the criteria above that occur before Cycle 2 Day 1 administration. TEAEs meeting DLT definitions occurring in later cycles will determine the suitability of the MTD as the RP2D.

Dose and schedule modifications for toxicity are described in Section 8.4.

8.3 Dose-Escalation Design and Criteria

8.3.1 Dose Levels

Patients will be enrolled in cohorts of 3 to 6, following a 3+3 dose escalation design.

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 300 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 600 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D.

[redacted]

Phase 2a

In the absence of DLT, the dose that will be administered in the subsequent phase 2a portion of the study will be based upon a comprehensive review of available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study.

8.3.2 Escalation Schema

A 3+3 dose escalation schema will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

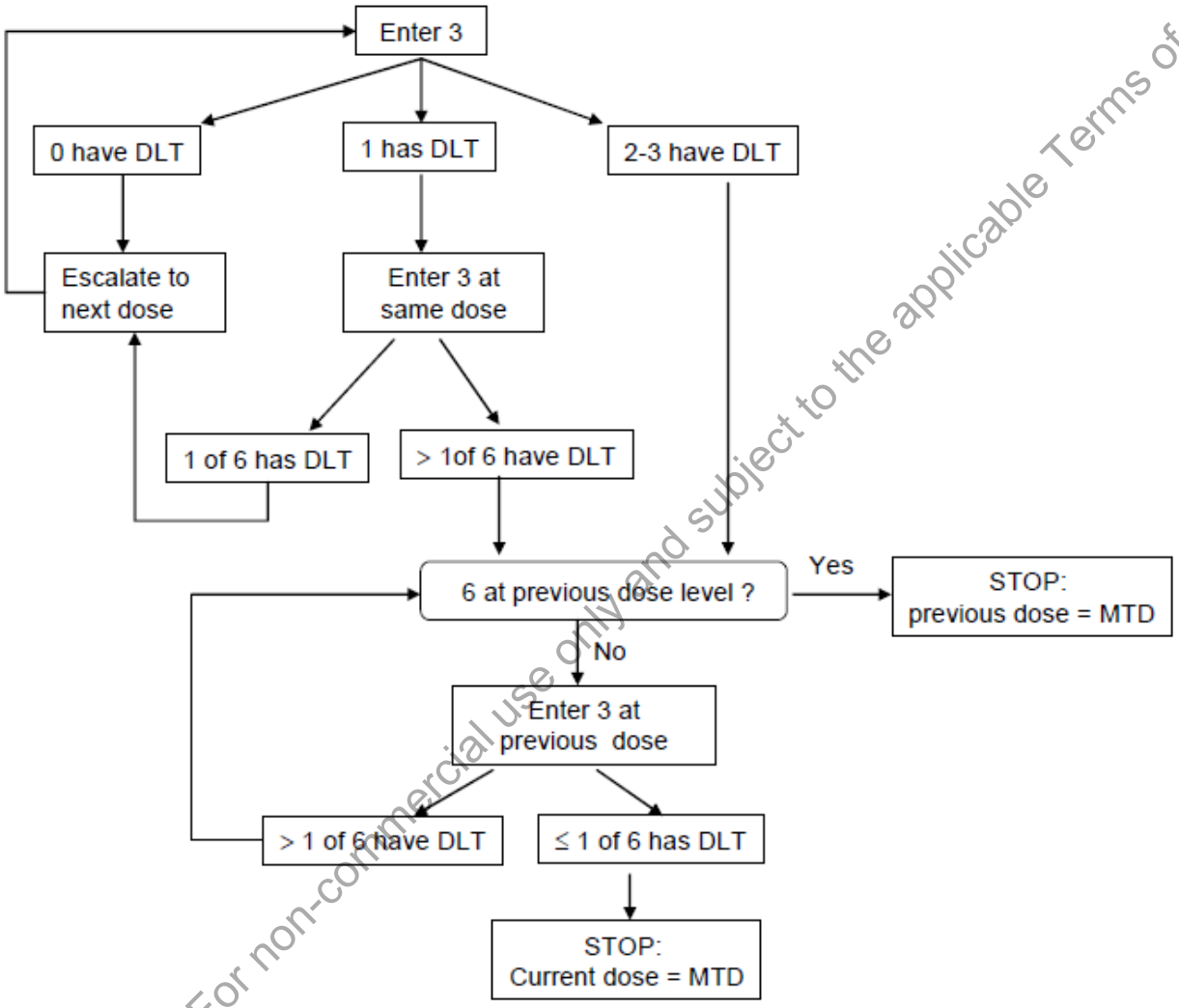
[redacted]

- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
- If ≤1 of 6 patients experiences a DLT, escalation will continue to the next higher dose level, at which 3 patients will be enrolled.
- If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3 patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and the lower dose level may be considered the MTD.

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm.

[redacted]

Figure 8.a Dose-Escalation Scheme



DLT=dose-limiting toxicity.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or [redacted].

Before initiating the dosing of the next cohort, when safety data are available for all patients in the current cohort, key safety data will be reviewed and evaluated by the study team consisting of sponsor representatives and investigators who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, changes to the dose-escalation scheme or dose schedule (dosing interval) may be considered. All decisions will be documented in writing. Any decision to modify the dose-escalation scheme (with the exception of testing intermediate

[redacted]

dose levels) or dose schedule will be communicated to institutional review boards (IRBs), and the protocol will be amended accordingly.

8.4 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for TAK-079 on the basis of the type and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

8.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with TAK-079 will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- Absolute neutrophil count must be $\geq 1000/mm^3$.
- Platelet count must be $\geq 75{,}000/mm^3$.
- For therapy to resume, toxicity considered to be related to treatment with TAK-079 must have resolved to Grade ≤1 or baseline, or to a level considered acceptable by the physician. If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If there is a delay of a subsequent cycle longer than 2 weeks because of a drug-related AE, 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. TAK-079 dosing may be continued at the previously established safe dose level or below.
- For TAK-079 injections within the same cycle, the decision of holding treatment is left to the investigator's discretion based on clinical and analytical data, and also based on the toxicity that the patient experienced with previous injections in the same cycle. The investigator should differentiate between acute toxicity (like an IR) from which the patient is recovered at the time of the next injection, and subacute toxicity (for example, neutropenia) that might be worsened upon another injection if it is not on a clear recovery path. If the dose cannot be administered on the scheduled day, the patient can be reviewed at the investigator's discretion in the following 48 hours. If TAK-079 cannot be administered within a cycle in this 48-hour window, the dose will be missed and the patient scheduled for the next administration per the Schedule of Events (SOE; Appendix A).

8.4.2 Criteria for Dose Reduction

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held, may have their dose reduced, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after

resolution of the AE at the same dose level or at a reduced dose, 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 study drug may be treated as per local standard of care, dose-modifications, interruptions and permanent discontinuations may be discussed upfront with the medical monitor.

Table 8.a provides general dose modification recommendations. When the dose of TAK-079 is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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. See details for managing specific AEs in Section 8.8.

Table 8.a Dose Modification Recommendations for TAK-079 Toxicities

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same or a reduced dose is 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 or, depending on the toxicity, at the previous safe dose level or below.
Grade 3 AEs	Patients with Grade 3 AEs considered related to study treatment should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline, then resume treatment at a reduced dose level.
Grade 4 (life-threatening) AEs	Patients with Grade 4 AEs considered related to study treatment should permanently discontinue treatment.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment can be resumed at a reduced dose level after resolution of AEs to Grade ≤1 or baseline.

AE=adverse event.

When a dose reduction occurs, the TAK-079 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-079 can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-079 because of AE are generally recommended.

If dose-reduction is not possible because the lowest dose-level has already been reached, treatment may be permanently discontinued.

The dose of TAK-079 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

8.4.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification)

TAK-079 should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that re-treatment of the patient could be dangerous. For Grade 4 (life-threatening) TEAEs, consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit, there are opportunities to provide supportive care to mitigate risk for the Grade 4 event to reoccur, and this approach (ie, the specific situation and mitigation plan) has been discussed with the sponsor. In these circumstances, treatment may be restarted at the previously safe dose level or below when toxicity recovers to Grade ≤1 or baseline.

If the next cycle of TAK-079 is delayed for >14 days because of TAK-079–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 occurs, the end of treatment (EOT)/early termination visit should be completed and the follow-up visit should occur within 30 (±7) days after the last administration of TAK-079. Additional details for study treatment discontinuation are provided in Section 9.7.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy and radiation therapy for the disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor's medical monitor and once PD is ruled out.
- Systemic corticosteroid use >10 mg/day (prednisone or equivalent).
- Live vaccines.
- Any investigational agent other than TAK-079, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.

8.6 Permitted Concomitant Medications and Procedures

- All necessary supportive care consistent with optimal patient care will be available to patients as necessary. All blood products and concomitant medications received from the first dose of the study drug regimen until 30 days after the final dose will be recorded in the electronic case report forms (eCRFs).
- The following medications and procedures are permitted while the patient is receiving the study drug:

[redacted]

- Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent).
- Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice.
- Transfusions with RBCs and platelets as clinically indicated; localized radiation for pain management for osteolytic lesions.
- Concomitant treatment with bisphosphonates will be encouraged for all 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. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.
- Topical or inhaled steroids and short-acting β_2 adrenergic receptor agonists (eg, for the treatment of asthma) are permitted.
- Nonresorbable corticosteroids (eg, budesonide).
- Plasmapheresis.

8.7 Precautions and Restrictions

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

NSAIDs should be avoided with impaired renal function given the reported NSAID-induced renal failure in patients with decreased renal function.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-079 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following:

- WOCBP must not be pregnant or lactating.
- 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 5 half-lives after the last dose of study drug (whichever is longer), OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and 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 one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium, and uric acid levels must be performed. Patients with tumor lysis syndrome should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis as indicated).

8.8 Management of Specific Adverse Reactions

8.8.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of Grade 1 or 2 infusion reactions:

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.

In case of Grade 3 infusion reactions:

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached and therefore skip remaining dose) until next scheduled TAK-079 SC administration, providing that infusion reactions have recovered to Grade ≤1 at the moment of the next scheduled TAK-079 dose.
- Permanently discontinue treatment after the 3rd occurrence of Grade 3 infusion reactions

In case of Grade 4 infusion reactions:

- Permanently discontinue treatment.

In case of an IR, blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

For additional details, refer to Section 9.4.15.3.

8.8.2 Handling of Low Platelet Counts

Treatment decisions will be based on patient platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled treatment to be postponed or to be permanently discontinued. If at any time the platelet count is less than 10×10^9/L, or if the patient shows a bleeding tendency considered to be due to thrombocytopenia occurring after initiation of TAK-079 treatment, the patient should be withdrawn from TAK-079 treatment. Platelet transfusion and daily monitoring of platelet counts are recommended. These patients should be considered as having experienced an SAE.

8.8.3 Risk of Infection

The intended mechanism of action of TAK-079 may involve reduction of the subject's immune response. Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis treatment may be initiated as clinically indicated, as determined by the investigator. Patients during the study should be followed closely for signs and symptoms of infection and treated as clinically indicated.

Until more clinical experience is gained with the use of TAK-079, it is prudent to avoid situations that may place subjects at increased risk of infection.

8.8.4 Transfusion Risks

Blood samples from patients being treated with TAK-079 may show pan reactivity during pretransfusion testing. To facilitate the provision of blood components for such patients, it is recommended that a baseline phenotype or genotype be established before starting treatment with TAK-079. Patients should keep this information in case future transfusions are needed. If a patient requires RBC phenotyping after the start of TAK-079 treatment, dithiothreitol treatment of the patient's RBCs should be performed, in case of preexisting positivity to standard tests.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

[redacted]

[redacted]

8.11 Preparation, Reconstitution, and Dispensation

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

TAK-079 is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling TAK-079.

8.12 Packaging and Labeling

Supplies of TAK-079 will be labeled according to the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

8.13 Storage, Handling, and Accountability

8.13.1 Storage and Handling

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label.

During shipping, vials will be protected from light and maintained below -15°C (5°F). Each TAK-079 shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

[redacted]

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

The investigator is responsible for ensuring that deliveries of TAK-079 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Detailed dosage preparation instructions are provided in the Directions for Use section of the Pharmacy Manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the Pharmacy Manual.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the Pharmacy Manual.

8.13.2 Accountability and Destruction of Sponsor Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

[redacted]

The investigator must maintain 100% accountability for all study medication (TAK-079) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative, otherwise uninvolved with study conduct, will review the subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication. This review will be documented at the site.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Empty, partially used, and unused TAK-079 will be disposed of, retained, or returned to the sponsor or designee.

The investigator must maintain a current inventory (Drug Accountability Log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and subjects' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

8.14 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned using an 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 numbers (MED IDs) 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.

[redacted]

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory, and any additional clinical laboratories, the coordinating investigator for each member state/country, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC). The screening period for this study is 21 days.

9.3 Treatment Group Assignments

All patients will receive open-label treatment with TAK-079 as indicated in respectively assigned treatment cohorts.

9.4 Study Procedures

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. This includes initial diagnosis date and MM staging at initial diagnosis using the International Staging System and Salmon-Durie Staging. Before dosing, the investigator should select the International Staging System, which should be consistently used throughout the study.

Known cytogenetic alterations should also be collected. Prior treatment regimens, with each treatment duration (start and stop dates), and the best response obtained with each therapy should be recorded. Refractoriness to previous treatments should be collected following IMWG criteria

(Appendix E). Confirm that the patient's current medical status does not include active chronic HBV, HCV, CMV, or HIV infection.

For patients who have received previous anti-CD38 therapy, the worst grade of infusion-related reactions should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured during the Screening Visit only. Weight will be measured on Day 1 of each treatment cycle, as indicated in Appendix A.

9.4.6 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital sign measurements will be made before TAK-079 injection and include supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position). All measurements should be performed in the same initial position, including heart rate and body temperature.

Blood pressure will also be measured before each injection, and at any time the patient complains of symptoms consistent with IR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Vital signs will be measured at the visits specified in the SOE (Appendix A). 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 10.2.

9.4.7 Eligibility Criteria

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.

9.4.8 Pregnancy Test

WOCBP must have 2 negative pregnancy tests (human chorionic gonadotropin >5 mI/mL) prior to starting study drug. A serum pregnancy test will be used during the screening period (within 10 to 14 days before the start of study drug). A serum pregnancy test must also be performed at baseline (within 24 hours before the start of study drug). A WOCPB is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential)

for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

During the study, if a menstrual period is delayed, absence of pregnancy in WOCBP must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study upon request by an IRB or if required by local regulations.

A urine pregnancy test is required in WOCBP at designated treatment visits (Appendix A) and also at the follow-up visit.

9.4.9 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had within 21 days before TAK-079 administration and up to 30 days after the last dose of TAK-079 (or the start of subsequent anticancer therapy, whichever occurs first) will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF. See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.10 AEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.4.11 Enrollment

A patient is considered to be enrolled in the study at the first injection.

Procedures for completing the enrollment information are described in the Study Manual.

9.4.12 ECG

A single ECG will be collected at the screening visit for assessment of eligibility. A qualified person will interpret the ECG.

Time-matched triplicate 12-lead ECGs and PK samples will be collected in this study during Cycles 1 and 2 as specified in Appendix B. Although the number of scheduled ECG measurements will not be increased, the timing may be changed if emerging data indicate that an alteration in the ECG schedule is needed. Triplicate ECGs will be recorded electronically and transmitted to a central vendor for storage.

The triplicate ECG measurements should be completed before the PK blood draw. Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement.

[redacted]

Single, 12-lead ECGs will be administered at all other designated visits (ie, after Cycle 2), as specified in Appendix A.

Any ECG finding that is judged by the investigator as clinically significant (except at the Screening Visit) will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally (includes the direct and indirect Coombs tests). Exceptions are discussed below.

Handling of clinical laboratory samples will be outlined in the Study Manual. [redacted] and immunogenicity (ADA and potential neutralizing antibodies [NAB]) assessments are to be performed centrally.

CD38 expression will be assessed by multicolor flow cytometry, and patients who express CD38 with a mean fluorescence intensity ≥1000 units on ≥90% of plasma cells will be eligible for inclusion into the trial. [redacted] CD38 expression will be assessed locally for both phase 1 and phase 2a for enrollment into the study then confirmed centrally.

[redacted]

Decisions regarding eligibility for this study may be made using local laboratory determinations in the dose-escalation portion of phase 1 of this study. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

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

[redacted]

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
ANC	Albumin	Creatinine clearance
Hematocrit	ALP	CRP
Hemoglobin	ALT	Glucose (nonfasting)
Platelet (count)	AST	GGT
Reticulocyte count	Bilirubin (total)	LDH
RBC count	BUN	Phosphate
WBC count	Calcium	Potassium
WBC with differential	Chloride	Sodium
Coagulation panel	CO_2 (bicarbonate)	Total protein
	Creatinine	Urate (uric acid)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=serine aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=γ-glutamyl transferase; LDH=lactate dehydrogenase RBC=red blood cell; WBC=white blood cell.

Table 9.b Clinical Urinalysis Tests

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

For estimation of creatinine clearance, the Cockcroft-Gault formula will be employed as follows:

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

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

9.4.13.2 Prestudy Prognostic Risk Assessment

A blood sample will be collected for serum β_2 microglobulin at screening to assess patient disease status. Results will be analyzed locally.

9.4.14 Disease Response Assessments

Patients will be assessed for disease response according to the IMWG for MM ([9,10]; Appendix E).

Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079.

[redacted]

Imaging tests as specified in Appendix A are to be performed as defined below or when there is a need to document a response or a disease progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase prior to treatment and every 6 cycles thereafter until PD or intolerance. Additional surveys (x-ray, CT, or MRI) will be performed at the investigator's discretion (eg, in case of bone pain) to document a response or progressive disease. The same imaging technique should be used throughout the study to facilitate consistent disease assessment.

CR should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.

Note that to determine a response of sCR, BMA immunohistochemistry or immunofluorescence for kappa:lambda ratio, as well as serum FLC assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

PD may be confirmed per standard clinical practice at the site. Local laboratory results may be used to confirm PD.

9.4.14.1 Computed Tomography/Magnetic Resonance Imaging

For patients with documented extramedullary disease, a whole body x-ray, positron emission tomography-computed tomography (PET-CT) scan, computed tomography (CT) scan (includes low-dose CT), or magnetic resonance imaging (MRI) scan will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, that image be used as baseline and does not need to be repeated as part of screening) as needed for evaluation of disease. If disease is documented, then a repeat PET-CT scan, CT scan, or MRI scan should be performed as required to document response or PD.

Scans will be performed at screening and at the EOT/early termination visit. All treatment phase and follow-up scans should use the same imaging modality used at screening.

Surveys (x-ray, CT, or MRI) may also be performed at the investigator's discretion, eg, in case of bone pain. The screening scan may be performed up to 21 days before first dose of TAK-079. Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.4.14.2 Quantification of Immunoglobulins

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained at the screening visit, predose on Day 1 of every cycle, and at the follow-up visit. Analysis of Ig will be performed locally.

9.4.14.3 Quantification of M-Protein

A predose blood and 24-hour urine sample will be obtained at the screening visit, Day 1 of every cycle, and at the follow-up visit. Urine sampling at designated time points is required only if urine M-protein is measurable at Day 1.

The samples will be tested locally. M-protein in serum and urine will be quantified by SPEP and UPEP.

9.4.14.4 Serum FLC Assay

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, and at the follow-up visit for the serum FLC assay (including quantification of kappa and lambda chains and ratio). Blood samples will be analyzed locally.

9.4.14.5 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, at the follow-up visit, and to confirm CR. Immunofixation testing will be performed in a local laboratory.

9.4.14.6 BMAs

BMAs will be taken during the screening period and at the beginning of designated study visits at Cycles 2, 4, 7, and every 6 cycles thereafter (ie, 13, 19, 25, etc.) until PD or intolerance, as described in Appendix A for the BMA measurements. Requirements for BMA assessments to confirm disease responses are defined at the beginning (Section 9.4.14).

Central Laboratory Evaluations

Molecular Analyses and Cytogenetics
The sample of BMA obtained at screening will be used for molecular analyses and for evaluation of cytogenetics. For response assessment purposes, when a CR is suspected on laboratory values, a BMA is required to confirm a CR as per routine clinical practice. At the time of this procedure, 1 sample is analyzed locally for evaluation of disease, while a separate aspirate sample must be sent directly to the central laboratory on the day of collection in accordance with the procedures outlined in the Study Manual/Laboratory Manual.

It is also highly encouraged (optional) to perform an aspiration procedure for the same purpose in patients who achieve PR as best response.

An aspirate for molecular analysis will also be collected at the time of disease relapse. This sample will be collected at the time of PD confirmation, before starting a new therapy, and will be sent to the central laboratory for analysis.

Local Laboratory Evaluations

Disease Assessment

A BMA will be obtained at screening for disease assessment and at any time a BMA sample is obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally. Determination of the kappa:lambda ratio by immunohistochemistry or immunofluorescence should be performed to assess for sCR when CR has been documented.

A standard BMA drawn before consent is acceptable provided it is collected within 5 weeks prior to the first dose.

Cytogenetics

If a sufficient sample is available at screening, an additional BMA or bone marrow sample may also be submitted for cytogenetic evaluation to be analyzed locally, according to local standards, if the site has the capability to perform the analysis. These analyses should be performed at screening using fluorescence in situ hybridization and/or conventional cytogenetics (karyotype). The central laboratory cytogenetic results will be used for study analysis, whereas local laboratory cytogenetic results (where available) will be used only in instances when central laboratory results are not available.

9.4.15 [redacted], PK, [redacted], and Immunogenicity Samples

9.4.15.1 Primary Specimen Collection for PK, [redacted], and [redacted] Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix B for the measurement of serum concentrations of TAK-079 and in Appendix A for [redacted].

The primary specimen collection is presented in Table 9.c. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for TAK-079 PK	Serum	PK measurements	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
Serum sample for immunogenicity	Serum	Immunogenicity assessments	Mandatory
Serum sample for direct and indirect Coombs test	Serum	Immunogenicity assessments	Mandatory

PK=pharmacokinetics.

9.4.15.2 PK Measurements

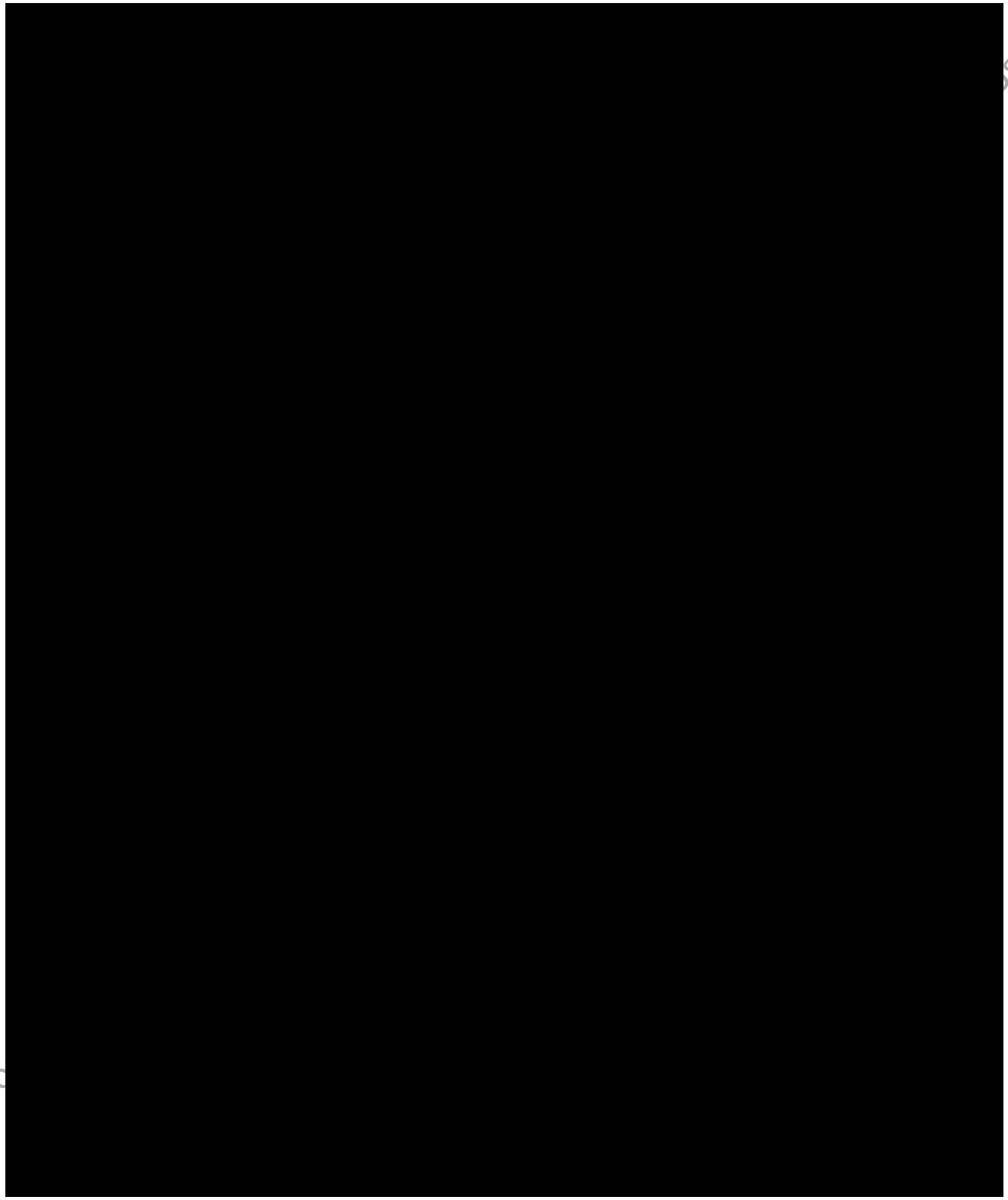
Serum samples for the measurement of concentrations of TAK-079 will be collected at multiple time points as specified in Appendix B.

The timing, but not the total number, of samples may be modified during the study on the basis of emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual.

9.4.15.3 [redacted]

[redacted]



[redacted]

9.4.15.4 Immunogenicity Assessments

ADA Assessment

Serum samples for the assessment of anti–TAK-079 immunogenicity will be collected at the study visits specified in Appendix A. A blood sample will be collected before administration of TAK-079 (ie, prior to dosing on Day 1; baseline value), then subsequently before TAK-079 dosing at each designated visit (postbaseline values), and at visits for any patient who experiences a TEAE considered by the investigator to be consistent with hypersensitivity/IR.

A sample will initially be screened for ADA titer. If a sample is detected as ADA positive, it may be assessed for neutralizing activity.

Direct and Indirect Coombs Testing

Serum samples for direct and indirect Coombs testing will be collected at time points specified in Appendix A. These tests will be performed locally.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered as having completed study treatment if they discontinued study drug for any reason as outlined below in Section 9.7.

9.6 Completion of Study (for Individual Patients)

Patients will receive TAK-079 until they experience PD, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor (see additional details in Section 9.8).

[redacted]

Patients will have a follow-up visit 30 days after the last dose of study drug or prior to the start of subsequent alternative anticancer therapy, to permit the detection of any delayed AEs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

Patients will be followed every 12 weeks for OS until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

It is anticipated that the duration of the study will be approximately 48 months (4 years).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.
- Withdrawal by patient.
- Female patient has confirmed pregnancy.

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

- AE/SAE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.

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

In phase 1, patients who do not receive 4 full doses of TAK-079 within the 28-day (±2) treatment window or the Day 29 (ie, Cycle 2 Day 1) assessment for reasons other than a DLT will be replaced. In phase 2a, patients who receive 1 or more injections of study drug will not be replaced.

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

[redacted]

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 by patient (mandatory immediate discontinuation of study agent).
- Death.
- PD.

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

9.9 Study Compliance

Study drug will be administered 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 stop treatment for any reason other than progressive disease will continue to have progression-free follow-up visits (additional details in Section 9.6). Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD, whichever occurs first.

Patients who stop treatment due to PD will continue to have OS visits. Patients will be followed every 12 weeks for OS after documented PD until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD, 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.

See the SOE (Appendix A) for appropriate assessments during follow-up.

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

[redacted]

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 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 4.03, effective date 14 June 2010 [12]. 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 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 <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 and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

Cognizant
United States and Canada
Toll-free fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

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

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

pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [12]. 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.

SAEs:

- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 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 caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who

identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

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

Product	Call Center	Phone Number	E-mail	Fax
TAK-079	DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2)

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

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

[redacted]

11.0 STUDY-SPECIFIC COMMITTEES

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

[redacted]

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of

a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

[redacted]

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of TAK-079.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-079 and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of TAK-079.

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, and DOR.

[redacted]

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient dosing data and TAK-079 concentration-time data to permit the calculation of PK parameters.

Immunogenicity analysis set: The immunogenicity analysis set will include those patients from the safety population who have baseline and at least one postbaseline sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. 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 if necessary.

[redacted]

13.1.3 Efficacy Analysis

Data from any efficacy assessments performed after the specified follow-up time will not be collected on the eCRF; if such data are collected, these data will not be analyzed.

The preliminary efficacy of TAK-079 for MM will be evaluated by measuring the ORR defined as the proportion of patients who achieved a PR or better during study; the composition of sCR, CR, very good partial response (VGPR), and PR as defined by the IMWG Uniform Response Criteria (see Appendix E).

In addition, the efficacy of TAK-079 will be assessed in patients by measuring DOR, PFS (PD will be defined by IMWG criteria), and 1-year OS. TTR will also be measured.

13.1.4 PK Analysis

PK parameters will be estimated using noncompartmental analysis methods. Parameters will be calculated for individual patients included in the PK analysis set using the TAK-079 concentration-time data. The calculated PK parameters will include, but not be limited to, C_{max}, t_{max}, and AUC_{last} (as permitted by the data).

PK parameters will be summarized using descriptive statistics. Individual TAK-079 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 PK data collected in this study may also contribute to future population PK analyses of TAK-079. These population PK analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Similarly, the time-matched PK and triplicate ECG data collected in this study may contribute to future concentration-QT interval corrected for heart rate (QTc) analyses. These analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the concentration-QTc analysis will be separately defined, and the results will be reported separately.

13.1.5 [redacted]

[redacted]

13.1.6 Immunogenicity Analyses

TAK-079 immunogenicity will be analyzed using the immunogenicity analysis set. The proportion of patients with positive ADA (transient and persistent) will be summarized, and the proportion of patients in phase 2a with positive neutralizing ADA during the study may be

[redacted]

summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined. NABs may also be assessed in patients.

The immunogenicity of TAK-079 will be assessed by determining anti–TAK-079 antibody incidence and characteristics (eg, titer, transiently, and persistently ADA; and possible neutralizing activity). Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-079 antibodies on the PK profile, drug efficacy, and clinical safety will be evaluated, if possible.

13.1.7 Safety Analysis

The safety and tolerability of TAK-079 will be assessed by the recording and analysis of TEAEs (NCI CTCAE version 4.03; [12]), vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, and concomitant medications.

TEAEs will be summarized using the safety analysis set and will be coded using the MedDRA. Data will be summarized using preferred term and primary system organ class.

In the phase 2a portion of this study, Grade 4 or higher nonhematological toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients. If the stopping bounds of ≥4/10 and ≥6/20 have been reached, accrual to the study will be suspended to allow for investigation. After consideration by the study team, a decision will be made as to whether accrual can be resumed. The bounds 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 18% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate [13].

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately 18 patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with r/r MM.

A 3+3 dose escalation schema will be used for dose escalation as described in Section 8.3.2.

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile.

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and [redacted] before the phase 2a of this study is opened to enrollment. Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 24.

[redacted]

In phase 2a, up to a total of 18 patients will be treated to provide a preliminary estimate of the ORR in patients with r/r MM. All patients must show a clear evidence of PD with anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 13.a shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this relapse/refractory population.

Table 13.a 80% Confidence Interval Based on the Observed ORR

[redacted]

N=18 patients.
ORR=overall response rate.

[redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. 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 federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

[redacted]

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

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

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

[redacted]

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

15.3 Patient Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

[redacted]

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 in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's 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 to find 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 callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, 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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

[redacted]

16.0 REFERENCES

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Appendix A Schedule of Events

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Informed consent (b)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
HBV, HCV, CMV, and HIV	X								
Height and weight (c)	X	X				X			
ECOG performance status	X	X				X			
ECG (d)	X	X				X			
		ECG measurements additionally on **Days 2, 3**, and **4** for Cycles 1 and 2 (see Section 9.4.12).							
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).								
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).								
Dosing									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 injection (f)		X	X	X	X	X	X	X	X
Laboratory assessments									
Serum chemistry (g)	X	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X	X

Footnotes added on last page of SOE tables.

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2 (continued)

Study Period (Phases 1 and 2a)	Screen-ing (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Urinalysis (i)	X	X	X	X	X	X	X	X	X
Pregnancy test (j) (k)	X	X				X			
Response assessments for MM									
Serum M-protein	X	X				X			
Urine M-protein (l)	X	X				X			
Serum FLC assay (m)	X	X				X			
Immunofixation - serum and urine (n)	X	X				X			
Quantification of Ig	X	X				X			
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)	X								
Biological assessments									
Bone marrow aspiration (BMMCs) (p)	X					X			
Serum sample for TAK-079 PK (q)		X	X	X	X	X	X	X	X
		PK sampling additionally on **Days 2, 3**, and **4** for Cycles 1 and 2.							
[redacted]									
Serum sample for immunogenicity (ADA/titer) (s)		X		X		X			
[redacted]									
Serum sample for direct and indirect Coombs test(s)	X	X				X			

Footnotes added on last page of SOE tables.

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Treatment Period Continued: Cycles 3 Through 6

	Treatment Phase (Every 2 Weeks)							
Study Period (Phases 1 and 2a)	**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Height and weight (c)	X		X		X		X	
ECOG performance status	X		X		X		X	
ECG (d)	X		X		X		X	
Physical examination	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).							
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).							
Dosing								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 injection (f)	X	X	X	X	X	X	X	X
Laboratory assessments								
Serum chemistry (g	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X	X	X	X	X	X	X
Pregnancy test (j) (k)	X		X		X		X	
Response assessments for MM								
Serum M-protein	X		X		X		X	
Urine M-protein (l)	X		X		X		X	
Serum FLC assay (m)	X		X		X		X	
Immunofixation - serum and urine (n)	X		X		X		X	

Footnotes added on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 3 Through 6 (continued)

	Treatment Phase (Every 2 Weeks)							
Study Period (Phases 1 and 2a)	**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Quantification of Ig	X		X		X		X	
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)							X	
Biological assessments								
Bone marrow aspiration (BMMCs) (p)			X					
Serum sample for TAK-079 PK (q)	X	X	X	X	X	X	X	X
[redacted]								
Serum sample for immunogenicity (ADA/titer) (s)	X		X		X		X	
[redacted]								
Serum sample for direct and indirect Coombs test (s)	X		X		X		X	

Footnotes added on last page of SOE tables.

Treatment Period: Cycles 7 to Follow-up and Overall Survival Follow-up

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase		
					Survival	
Study Period (Phases 1 and 2a)	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	Follow-Up Visit	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	**C7D1**	**C8D1, CXD1**		--------	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Laboratory assessments						
Height and weight (c)	X	X	X	X		
ECOG performance status	X	X	X	X		
ECG (d)	X	X	X	X		
Physical examination	X	X	X	X		
Vital signs (e)	X	X	X	X		
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.					
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3). **SAEs** (includes pretreatment and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).					
Dosing						
Pre-injection medication	X	X	X			
TAK-079 injection (f)	X	X	X			
Laboratory assessments						
Serum chemistry (g)	X	X	X	X		
Hematology (h)	X	X	X	X		
Urinalysis (i)	X	X	X	X		
Pregnancy test (j) (k)	X	X	X	X		
Response assessments for MM						
Serum M-protein	X	X	X	X		
Urine M-protein (l)	X	X	X	X		
Serum FLC assay (m)	X	X	X	X		

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Treatment Period: Cycles 7 to Follow-up and Overall Survival Follow-up (continued)

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase		
					Survival	
Study Period (Phases 1 and 2a)	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	Follow-Up Visit	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	**C7D1**	**C8D1, CXD1**		--------	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Immunofixation - serum and urine (n)	X	X	X	X		
Quantification of Ig	X	X	X	X		
Skeletal survey: WB X-ray, CT, low dose CT, PET-CT, or MRI scan (o)			X			
Biological assessments						
Bone marrow aspiration (BMMCs) (p)	X					
Serum sample for TAK-079 PK (q)	X	X	X			
[redacted]						
Serum sample for immunogenicity (ADA/titer) (s)	X	X	X	X		
[redacted]						
Serum sample for direct and indirect Coombs test (s)	X	X	X	X		
Disease status assessment (u)					X	
Survival (v)						X

Footnotes added on last page of SOE tables.

[redacted]

ADA=antidrug antibody; AE=adverse event; ALP=alkaline phosphatase ;ALT=alanine aminotransferase ; ANC=absolute neutrophil count ; AST=aspartate aminotransferase; BMA=bone marrow aspirate; BMMCs=bone marrow mononuclear cells; BUN=blood urea nitrogen; C=cycle; CMV=cytomegalovirus; CR=complete response; CT=computed tomography; CXD1=Day 1 of additional treatment cycles (ie, after Cycle 8); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FLC=free light chain; GGT=gamma glutamyl transferase; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=Informed Consent Form; Ig=immunoglobulin; IR=injection reaction; LDH=lactate dehydrogenase; LPLV=last patient last visit; MM=multiple myeloma ; MRI=magnetic resonance imaging; OS=overall survival; PD=disease progression; PET-CT=positron emission tomography-computed tomography; PFS=progression-free survival; PK=pharmacokinetics; RBC=red blood cell(s);SAE=serious adverse event(s); SOE=Schedule of Events; V=visit; WB=whole body; WBC=white blood cell(s).

(a) The screening period is 21 days (ie, Days -21 to Day -1).

(b) Written informed consent must be obtained before performing any protocol-specific procedure.

(c) Height will be measured only at the Screening Visit. Weight will be measured at indicated visits.

(d) A single ECG will be collected at the screening visit. PK time-matched triplicate 12-lead ECGs will be collected during Cycles 1 and 2, as specified in Appendix B. Single 12-lead ECGs will be administered for all other designated visits (ie, after Cycle 2).

(e) Vital signs are measured prior to TAK-079 injection. Blood pressure will also be measured before starting each 2 mL injection, and at any time the patient complains of symptoms consistent with IR. Vital signs include temperature, pulse, respiratory rate, and blood pressure.

(f) Time and anatomical site should be recorded for each injection.

(g) Serum β_2 microglobulin levels will be measured at screening only. Refer to Section 9.4.13.1 for a list of clinical chemistry laboratory assessments.

(h) Refer to Section 9.4.13.1 for a list of hematology laboratory assessments.

(i) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. Refer to Section 9.4.13.1 for a list of urinalysis assessments.

(j) Pregnancy test (Refer to Section 9.4.8): Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A serum pregnancy test will be performed during screening (within 10-14 days before start of study drug). A serum pregnancy test is required within 24 hours before start of study drug.

(k) Pregnancy test (refer to Section 9.4.8): On-treatment: a urine pregnancy test is required at designated study visits. A urine pregnancy test is required at the follow-up visit in women of childbearing potential. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.

(l) Sampling required only if urine M-protein is measurable at Day 1 (visit 2).

(m) Blood sample obtained for the serum FLC assay to include quantification of kappa and lambda chains and ratio). To be analyzed locally.

(n) Will also be collected to confirm a CR.

(o) May be performed up to 21 days before first dose of TAK-079. Surveys will also be performed at Cycle 6 and every 6 cycles thereafter until PD or intolerance. Additional surveys (x-ray, CT, or MRI) may be performed at the investigator's discretion, eg, in case of bone pain. If disease is documented, then a repeat scan should be performed as required to document a response or PD.

(p) BMAs: Samples will be taken during the screening phase, prior to treatment, and at the beginning of Cycles 2, 4, 7, and every 6 cycles (ie, 13, 19, 25, etc.) thereafter until PD or intolerance. At screening, a standard BMA drawn prior to consent is acceptable provided this is collected within 5 weeks before the first dose. For response assessment purposes, when a CR is suspected based on laboratory values, a BMA is required to confirm a CR. At the time of this procedure, 1 aspirate sample is analyzed locally for evaluation of disease, [redacted] It is also highly encouraged (optional) to perform an aspiration procedure in patients who [redacted]

[redacted]

(q) Blood samples for PK characterization will be collected at time points specified in Appendix B Pharmacokinetic Sampling Schedule.

[redacted]

(s) Serum samples for immunogenicity assessment will be collected at baseline (before TAK-079 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.

[redacted]

(u) Patients who discontinue treatment for reasons other than PD will continue to be followed every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.
(v) Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

[redacted]

Appendix B Pharmacokinetic Sampling Schedule

Pharmacokinetic Assessments: Cycle 1

	Cycle 1										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

Pharmacokinetic Assessments: Cycle 2

	Cycle 2										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

Pharmacokinetic Assessments: Cycle 3 to Cycle 10

	Cycle 3 to Cycle 6		**Cycle 7 to Cycle 10**
	Day 1 (a)	**Day 15 (a)**	**Day 1 (a)**
Predose (within 1 hour before first SC injection)	X	X	X

PK=pharmacokinetic; SC=subcutaneous.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.

[redacted]

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

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

[redacted]

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

[redacted]

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

[redacted]

Appendix E IMWG Criteria

IMWG Definition of MM

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically.
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of the normal range or >2.75 mmol/L (>11 mg/dL).
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL).
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡.
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%.
  - Involved: uninvolved serum free light chain ratio§ (FLC) ≥100.
  - >1 focal lesions on MRI studies.

* Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
† Measured or estimated by validated equations.
‡ If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, United Kingdom). The involved FLC must be ≥100 mg/L. Each focal lesion must be 5 mm or greater in size [14].

[redacted]

IMWG Uniform Criteria for Response

Category of Response	Response Criteria
sCR	Criteria for CR as defined below, with the addition of a normal FLC ratio, and an absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed (a).
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; 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; 2 consecutive assessments are needed (b).
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 >4 colors).
Molecular CR	CR as defined, plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; 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; 2 consecutive assessments are needed (c).
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed (a) no known evidence of progressive or new bone lesions if radiographic studies were performed.
Minimal response (MR) (b)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the 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 (c)	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

Source: Rajkumar SV et al, 2011 and Palumbo A et al, 2014 [9,10].
CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.
(a) Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

(b) For relapse-refractory myeloma only.
(c) These categories do not contribute to the ORR.

Before the institution of any new therapy, sCR, CR, and VGPR 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.

PD is defined as an increase of ≥25% from lowest response value in any of the following:

a) Serum M-protein (absolute increase must be ≥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

b) Urine M-protein (absolute increase must be ≥200 mg/24 hour), and/or

c) Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL).

d) Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%).

OR

a) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

b) Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Clarifications to IMWG criteria for coding PD: 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 tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

[redacted]

Appendix F ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM et al, 1982 [11].
ECOG=Eastern Cooperative Oncology Group.

[redacted]

Appendix G Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: The number of TAK-079 dose levels planned for phase 1 was changed to 6. The 400 mg dose level was removed, and the 300 and 600 mg dose levels were added.

The primary change occurs in Section 8.3.1 Dose Levels:

Initial wording:

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 400 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

[redacted]

Amended or new wording:

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- ~~400 mg~~ **300 mg**, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- **600 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.**
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

Rationale for Change:

This change was made in response to regulatory feedback from FDA regarding the dose escalation schedule in the original protocol.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 4.4.1 Rationale for the Starting Dose of TAK-079.
- Section 6.1 Overview of Study Design.
- Section 13.3 Determination of Sample Size.

[redacted]

Change 2: Planned enrollment was increased to 24 patients for the phase 1 portion (42 patients overall).

The primary change occurs in Section 6.2 Number of Patients:

Initial wording:	For phase 1, approximately 21 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 18 patients are planned.
Amended or new wording:	For phase 1, approximately ~~21~~ **24** patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 18 patients are planned.

Rationale for Change:

This change was made to reflect the revised number of planned dose escalation levels in the phase 1 portion of the study.

The following sections also contain this change:

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

Change 3: Eligibility based on laboratory criteria for determining adequate organ function was clarified for patients with Gilbert's syndrome.

The primary change occurs in Section 7.1 Inclusion Criteria Table 7.b Laboratory Criteria for Determining Adequate Organ Function for Study TAK-079-1501 Eligibility:

Initial wording:	Total serum bilirubin	≤1.5×ULN; an exception for patients with Gilbert's syndrome may be granted after discussion with the sponsor
Amended or new wording:	Total serum bilirubin	≤1.5×ULN; ~~an exception~~ **except** for patients with Gilbert's syndrome ~~may be granted after discussion with the sponsor~~ **in whom direct bilirubin should be <2.0×ULN**

Rationale for Change:

This change was made to clarify the bilirubin eligibility criteria for patients with Gilbert's syndrome.

[redacted]

Change 4: Inclusion criteria were modified to revise requirements for prior myeloma therapies and assessment of CD38 expression

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:

12. Previously received at least 2 lines of standard therapy (including both an IMiD and a PI), and is either refractory to or intolerant of at least one of these regimens. Prior treatment with an anti-CD38 mAb is allowed; however, CD38 expression must be significantly expressed on target cells for this mechanism of action to be effective.

Amended or new wording:

12. ~~Previously received at least 2 lines of standard therapy (including both an IMiD and a PI), and is either refractory to or intolerant of at least one of these regimens. Prior treatment with an anti-CD38 mAb is allowed; however, CD38 expression must be significantly expressed on target cells for this mechanism of action to be effective.~~ **Prior therapy should meet all of the following criteria:**
    - **Patient should be previously treated with at least a PI, an IMid, an alkylating agent, and a steroid.**
    - **Patient should be refractory or intolerant to at least 1 PI and at least 1 IMid.**
    - **Patient should either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMid.**
    - **Previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required.**
13. **Patients must express CD38 on target cells with a mean fluorescence intensity ≥1000 units on ≥90% of plasma cells as determined by multicolor flow cytometry.**

Rationale for Change:

This change was made in response to an FDA request to modify the inclusion criteria to evaluate a later line of prior therapy, to maintain enrollment with at least 3 lines of prior therapy given that single-agent lines of therapy are still available as treatment options, and to respond to an FDA request for further detail regarding assessment of CD38 expression.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 9.4.13 Clinical Laboratory Evaluations.

[redacted]

Change 5: [redacted]

The primary change occurs in Section 9.4.13 Clinical Laboratory Evaluations:

Added text: [redacted]

Rationale for Change:

This change was made to clarify [redacted]

Change 6: Exclusion criteria were modified to exclude patients with a higher risk of respiratory complications (chronic obstructive pulmonary disease with forced expiratory volume <80%).

The primary change occurs in Section 7.2 Exclusion Criteria:

Initial wording:	8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume <50%, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.
Amended or new wording:	8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume ~~<50%~~ **<80%**, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.

Rationale for Change:

This change was made in response to an FDA request to exclude patients at higher risk of respiratory complications.

Section 8.1.1 Premedication also contains this change.

[redacted]

Change 7: An exclusion criterion was added to exclude patients with positive Coombs tests at screening.

The primary change occurs in Section 7.2 Exclusion Criteria:

Added text: **20. Patients with positive Coombs tests at screening.**

Rationale for Change:

This change was made to exclude patients with persistent levels of daratumumab in the blood stream. Coombs positivity is induced by binding of daratumumab to CD38+ antigens on circulating red blood cells.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY

Appendix A Schedule of Events.

Change 8: The description of investigational agents was revised.

The primary change occurs in Section 8.10 Description of Investigational Agents:

Initial wording:	[redacted]
Amended or new wording:	[redacted] rubber stoppers and aluminum crimp seals with flip-off caps.

Rationale for Change:

[redacted]

Change 9: The definition of dose-limiting toxicities (DLTs) was modified to exclude relationship in determining a DLT, to include Grade 4 laboratory abnormalities clearly unrelated to the underlying disease as DLTs, and to note that events clearly due to extraneous causes will not be considered DLTs.

The primary change occurs in Section 8.2 Definitions of DLT:

Initial wording: DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with TAK-079.

- Nonhematologic TEAEs of NCI CTCAE Grade ≥3 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - Asymptomatic laboratory changes (other than renal and hepatic laboratory values, and Grade 4 lipase/amylase) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.
  - Grade 3 nausea/vomiting that can be managed subsequently with anti-emetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 72 hours.
  - Grade 3 elevation of ALT or AST that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms.
- Hematologic TEAEs of NCI CTCAE Grade ≥4 clearly unrelated to the underlying disease and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis clearly unrelated to the underlying disease (eg, negative direct Coombs test) will be included in the definition of DLT.
  - Grade 3 low platelet or higher count with clinically meaningful bleeding will be included in the definition of DLT.
  - Grade 4 low platelet count of duration <2 weeks will not be included in the definition of DLT.
  - Grade 4 lymphopenia will not be included in the definition of DLT.
- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a DLT.

[redacted]

Amended or new wording:

DLT**s** will be defined as any of the following events ~~that are considered by the investigator to be at least possibly related to therapy with TAK-079~~ **regardless of relationship, except those events that are clearly due to extraneous causes**.

- **Grade 4 laboratory abnormalities, except those events that are clearly due to extraneous causes, will be defined as a DLT.**
- Nonhematologic TEAEs of NCI CTCAE Grade ≥3 ~~clearly unrelated to the underlying disease~~**, except those events that are clearly due to extraneous causes,** and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - ~~Asymptomatic laboratory changes (other than renal and hepatic laboratory values, and Grade 4 lipase/amylase) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.~~
  - Grade 3 nausea/vomiting that can be managed subsequently with anti-emetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 72 hours.
  - Grade 3 elevation of ALT or AST that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms.
- Hematologic TEAEs of NCI CTCAE Grade ≥4 ~~clearly unrelated to the underlying disease~~**, except those events that are clearly due to extraneous causes,** and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis ~~clearly unrelated to the underlying disease~~**, except those events that are clearly due to extraneous causes** (eg, negative direct Coombs test)**,** will be included in the definition of DLT.
  - Grade 3 low platelet or higher count with clinically meaningful bleeding will be included in the definition of DLT.
  - ~~Grade 4 low platelet count of duration <2 weeks will not be included in the definition of DLT.~~
  - ~~Grade 4 lymphopenia will not be included in the definition of DLT.~~
- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a

DLT.

Rationale for Change:

This change was made in response to an FDA request for all AEs of specified grades to be counted as DLTs, regardless of investigator attribution or relatedness.

Change 10: The dose escalation schema was changed to a 3+3 design from a Bayesian logistic regression model.

The primary change occurs in Section 8.3.2 Escalation Schema:

Initial wording:

The Bayesian Logistic Regression Modeling (BLRM) method with overdose control will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

The following rules will apply only for this initial dose level:

- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
  - If no additional patient in the expanded cohort of 6 exhibits a DLT, then the dose may be escalated for the next cohort of 3 patients (pending approval following review of available safety data).
  - If a second (or more) patient in the expanded cohort of 6 exhibits a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped (pending BLRM approval following review of available safety data).
- If 2 or more patients in a cohort of 3 patients exhibit a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped.

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm for the first cohort.

Figure 8.a Dose-Escalation Scheme for Cohort 1

[Figure 8.a]

Once the dose is escalated above the starting dose level, BLRM will be used for all subsequent dose recommendations, along with consideration of other safety, clinical, PK, [redacted] data.

[redacted]

Amended or new wording:

~~The Bayesian Logistic Regression Modeling (BLRM) method with overdose control~~ **A 3+3 dose escalation schema** will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

~~*The following rules will apply only for this initial dose level:*~~

- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
  - ~~If no additional patient in the expanded cohort of 6 exhibits a DLT, then the dose may be escalated for the next cohort of 3 patients (pending approval following review of available safety data).~~
  - ~~If a second (or more) patient in the expanded cohort of 6 exhibits a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped (pending BLRM approval following review of available safety data).~~
- **If ≤1 of 6 patients experiences a DLT, escalation will continue to the next higher dose level, at which 3 patients will be enrolled.**
- ~~If 2 or more patients in a cohort of 3 patients exhibit a DLT, then that cohort will be deemed to have exceeded the MTD, and dose escalation will be stopped.~~ **If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3 patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and the lower dose level may be considered the MTD.**

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm ~~for the first cohort.~~

Figure 8.a Dose-Escalation Scheme ~~for Cohort 1~~

[Figure 8.a remains unchanged]

~~Once the dose is escalated above the starting dose level, BLRM will be used for all subsequent dose recommendations, along with consideration of other safety, clinical, PK, [redacted] data.~~

Rationale for Change:

This change was made in response to an FDA request to revise the dose escalation schema; by using the traditional 3+3 dose escalation schema, the selected dose would have a toxicity rate near 20% with range between 17% and 26% on average.

[redacted]

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 8.3.1 Dose Levels.
- Section 13.3 Determination of Sample Size.

Change 11: Dose modification recommendations in the event of Grades 3 and 4 adverse events were modified.

The primary change occurs in Section 8.4.2 Criteria for Dose Reduction Table 8.a Dose Modification Recommendations for TAK-079 Toxicities:

Initial wording:	Grade 3 AEs	Hold TAK-079 until resolution to Grade ≤1 or baseline, then resume treatment at either the same dose or a reduced dose level at the discretion of the investigator.
	Grade 4 (life-threatening) AEs	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor. Treatment may be restarted at a reduced dose level or below when toxicity recovers to Grade ≤1 or baseline.
Amended or new wording:	Grade 3 AEs	~~Hold TAK-079 until resolution~~ **Patients with Grade 3 AEs considered related to study treatment should have study treatment interrupted until the AE resolves** to Grade ≤1 or baseline, then resume treatment at ~~either the same dose or~~ a reduced dose level ~~at the discretion of the investigator~~.
	Grade 4 (life-threatening) AEs	~~Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor. Treatment may be restarted at a reduced dose level or below when toxicity recovers to Grade ≤1 or baseline.~~ **Patients with Grade 4 AEs considered related to study treatment should permanently discontinue treatment.**

Rationale for Change:

This change was made in response to an FDA request for the dose modification guidelines to be changed such that for Grade 3 nonhematologic toxicity, after resolution of the toxicity to Grade ≤1 or baseline, TAK-079 should be reduced by 1 dose level, and for Grade 4 nonhematologic toxicity, TAK-079 should be permanently discontinued.

[redacted]

Change 12: Instructions for handling infusion reactions were added to provide further instruction according to reaction grade.

The primary change occurs in Section 8.8.1 Handling of IRs:

Added text: **In case of Grade 1 or 2 infusion reactions:**

- **Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.**

In case of Grade 3 infusion reactions:

- **Withhold therapy (also administration of remaining SC injections when full dose was not yet reached and therefore skip remaining dose) until next scheduled TAK-079 SC administration, providing that infusion reactions have recovered to Grade ≤1 at the moment of the next scheduled TAK-079 dose.**
- **Permanently discontinue treatment after the 3rd occurrence of Grade 3 infusion reactions**

In case of Grade 4 infusion reactions:

- **Permanently discontinue treatment.**

Rationale for Change:

This change was made to clarify the handling of IRs.

Appendix A Schedule of Events, footnote (t), also contains this change.

Change 13: Methods for disease response imaging were clarified, including addition of a skeletal survey starting at Cycle 6.

The primary change occurs in 9.4.14 Disease Response Assessments.

Initial wording:	Imaging tests as specified in Appendix A are to be performed as defined below or when there is a clinical suspicion of progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase before treatment, at the beginning of Cycles 2, 4, 7, 13, 19, 25, and every 6 cycles thereafter until PD or intolerance.

[redacted]

Amended or new wording:	Imaging tests as specified in Appendix A are to be performed as defined below or when there is a ~~clinical suspicion of~~ **need to document a response or a disease** progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase ~~before~~ **prior to** treatment~~, at the beginning of Cycles 2, 4, 7, 13, 19, 25,~~ and every 6 cycles thereafter until PD or intolerance. **Additional surveys (x-ray, CT, or MRI) will be performed at the investigator's discretion (eg, in case of bone pain) to document a response or progressive disease. The same imaging technique should be used throughout the study to facilitate consistent disease assessment.**

Rationale for Change:

This change was made to correct and clarify disease assessments.

Appendix A Schedule of Events also contains this change.

Change 14: Text was added to the safety analysis methods regarding Grade 4 or higher nonhematologic toxicities occurring in the Phase 2a portion of the study.

The primary change occurs in 13.1.7 Safety Analysis:

Added text:	**In the phase 2a portion of this study, Grade 4 or higher nonhematological toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients. If the stopping bounds of ≥4/10 and ≥6/20 have been reached, accrual to the study will be suspended to allow for investigation. After consideration by the study team, a decision will be made as to whether accrual can be resumed. The bounds 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 18% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate [13].**

Rationale for Change:

This change was made in response to an FDA request to include for the Phase 2a portion overall study stopping rules that (1) are based on a specified rate of unacceptable toxicity, (2) include a definition of unacceptable toxicity, and (3) follow statistical principles to ensure that they apply to the entire population at various stages of study enrollment.

Section 2.0 STUDY SUMMARY also contains this change.

[redacted]

Change 15: [redacted]

The primary change occurs in 9.4.15.3 [redacted]

Initial wording:	[redacted]
Amended or new wording:	[redacted]

Rationale for Change:

This change was made to correct an error in the protocol.

Appendix A Schedule of Events contains this change.

Change 16: A serum sample for immunogenicity assessment was added on Cycle 1 Day 15.

The primary change occurs in Appendix A Schedule of Events:

Description of change:	In the row *Serum sample for immunogenicity (ADA/titer) (s)* an X was added to the *C1D15* column.

Rationale for Change:

This change was made to correct an error in the protocol.

Change 17: The pharmacokinetic sampling schedule was revised to reflect sample collection times relative to the first injection, rather than the final injection, when multiple injections are required to administer the intended dose. [redacted]

The primary change occurs in Appendix B Pharmacokinetic Sampling Schedule:

Description of change:

For Cycles 1 and 2, original text in Column 1:

Predose (within 1 hour before SC administration)

1 hour after SC administration (±15 min)

2 hours after SC administration (±15 min)

4 hours after SC administration (±30 min)

8 hours after SC administration (±1 hour)

24 hours after SC administration (±2 hours)

48 hours after SC administration (±2 hours)

72 hours after SC administration (±2 hours)

Was changed to:

Predose (within 1 hour before **first SC** ~~administration~~ **injection)**

~~1 hour~~ **5 minutes** after **FINAL** SC ~~administration~~ **injection** (~~±15~~ ±2 min) **(c)**

~~2~~ **4** hours after **first** SC ~~administration~~ **injection** (~~±15~~ ±30 min)

~~4~~ **6** hours after **first** SC ~~administration~~ **injection** (±30 min)

8 hours after **first** SC ~~administration~~ **injection** (±1 hour)

24 hours after **first** SC ~~administration~~ **injection** (±2 hours)

48 hours after **first** SC ~~administration~~ **injection** (±2 hours)

72 hours after **first** SC ~~administration~~ **injection** (±2 hours)

(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

For Cycle 3 to Cycle 10, original text in Column 1:

Predose (within 1 hour before SC administration)

Was changed to:

Predose (within 1 hour before **first** SC ~~administration~~ **injection**)

Additionally, the following footnote was deleted from the Cycle 3 to Cycle 10 table:

~~If multiple SC injections are required in order to administer the intended dose, post-dose PK assessments are to begin after administration of the final injection.~~

[redacted]

Rationale for Change:

This change was made to facilitate sample collection by revising the reference injection for assessment purposes to the first injection, rather than the final injection, when multiple injections are required to administer the intended dose.

The following sections also contain this change:

- Section 9.4.15.2 PK Measurements.
- Section 9.4.15.3 [redacted]
- Appendix A Schedule of Events

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	11-Dec-2017 15:53 UTC
[redacted]	Clinical Pharmacology Approval	11-Dec-2017 18:25 UTC

PROTOCOL

A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

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

Study Number: TAK-079-1501

IND Number: 136,414 **EudraCT Number:** Not applicable

Compound: TAK-079

Date: 18 May 2018 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Region
12 October 2017	Initial Protocol	Global
08 December 2017	01	Global
18 May 2018	02	Global

[redacted]

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.0 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
SAE and pregnancy reporting	See Section 10.0

[redacted]

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 on Harmonisation E6 Good Clinical Practice: 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]
Date
[redacted], MD, PhD
Global Medical Affairs
Distinguished Research Fellow Oncology

[redacted]
Date
[redacted], PhD
Global Statistics

[redacted]
Date
[redacted], RN, MSN
[redacted]
Oncology Clinical Research

[redacted]

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

[redacted]

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment 02. The primary reason for this amendment is to address inconsistency noted during review of Amendment 01. Local CD38 expression has been removed as an eligibility criterion, and time since last prior therapy with antineoplastic agents has been revised to align with clinical practice. Dose modification tables have been revised to align with other monoclonal antibodies where doses are withheld to manage toxicity rather than reduced; however, there is no change regarding management of patients who experience a dose-limiting toxicity (DLT) (patients may be permanently discontinued or if appropriate may receive a lower dose). Samples for exploratory translational medicine endpoints have been clarified for consistency throughout the protocol, with adjustments in the timing of samples to lessen patient burden. Other inconsistencies were also addressed, as noted in the specific changes below.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only. For specific descriptions of text changes and where the changes are located, see Appendix G.

Changes in Amendment 02

1. The study design was updated to reflect a maximum treatment duration of 12 months, unless a patient has clinical benefit that warrants continued treatment beyond 12 months.
2. Maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) was clarified to be a secondary objective/endpoint.
3. Time-to-event measures were added as a secondary objective.
4. [redacted]
5. Dosing procedures after Cycle 1 Day 1 in the setting of no systemic infusion reactions (IRs) were clarified.
6. Predose and postdose medications were clarified.
7. The periods of patient evaluation at end of treatment (EOT) and for progression-free survival (PFS) and overall survival (OS) were clarified throughout, including the estimated duration of the study and end-of-study reporting.
8. The time since last prior antineoplastic therapy was clarified.
9. [redacted]
10. Active cytomegalovirus infection was removed from the list of excluded infections.
11. Assessments of clinically significant laboratory values and vital signs were removed from the phase 1 primary endpoints as these are included in the definition of treatment-emergent adverse events (TEAEs).

[redacted]

12. Details on nonclinical studies with TAK-079 were added.
13. Details about management of IRs and injection site reactions were added.
14. The procedures for monitoring all infections were clarified.
15. The rationale for the proposed study was revised, including presentation of results from the healthy subject study.
16. The time required for highly effective contraception in women of childbearing potential (WOCBP) and in male patients was clarified for consistency.
17. The exclusion criterion about recovery from prior myeloma treatments was clarified to exclude alopecia.
18. DLT assessments and withdrawal/replacement of patients were clarified.
19. A sentence summarizing the definition of the MTD has been added.
20. The criteria for beginning or delaying a subsequent treatment cycle were clarified.
21. Disease response assessments, including imaging and laboratory testing, were clarified.
22. "Other" was added as a reason for treatment discontinuation or withdrawal of subject from study.
23. The time required to monitor ongoing adverse events (AEs) after the end of study treatment was clarified.
24. Investigator disease assessments were added to the Schedule of Events (SOE).

[redacted]

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LIST OF IN-TEXT TABLES

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LIST OF APPENDICES

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-079	
Title of Protocol: A Phase 1/2a, Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma		
Study Number: TAK-079-1501	**Phase:** 1/2a	

Study Design:

This is a multicenter, open-label, dose-escalation, single-arm, phase 1/2a study designed to determine the safety and tolerability of TAK-079 monotherapy in patients with relapsed and/or refractory multiple myeloma (RRMM), and to provide a preliminary assessment of its activity against RRMM.

Once enrolled into the study, patients will receive TAK-079 via subcutaneous (SC) administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until disease progression (PD). Patients will receive ongoing treatment with TAK-079 until PD, unacceptable toxicities, or withdrawal due to other reasons. The maximum duration of treatment will be 12 months; however, patients with clinical benefit (per investigator and as agreed upon by the sponsor's study clinician) can continue on treatment beyond 1 year with the explicit approval of the sponsor's study clinician (see Section 6.3).

The phase 1 portion of the study will evaluate administration of TAK-079 for dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) for further assessment in phase 2a. A recommended dose below the MTD may be identified based on the review of safety, pharmacokinetic (PK), [redacted], and clinical data from the phase 1 portion of the study.

The safety and tolerability of TAK-079 will be assessed by recording and analyzing treatment-emergent adverse events (TEAEs), dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology, urinalysis, electrocardiograms, and concomitant medications. In phase 1, approximately 6 doses of TAK-079 will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. In the phase 2a portion of this study, Grade 4 or higher nonhematologic toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients thereafter.

It is expected that approximately 42 patients will be enrolled in the study. The estimated duration of the study is approximately 36 months (ie, 3 years).

Primary Objectives:

Phase 1

To determine the safety and tolerability of TAK-079 monotherapy in patients with RRMM.

Phase 2a

To provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with RRMM.

Secondary Objectives:

Phase 1

- To investigate a potential MTD/RP2D of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

[redacted]

Phase 2a

- To further evaluate safety at the MTD/RP2D.
- To provide a preliminary evaluation of time-to-event measures.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

Exploratory Objectives:

Phase 1 and 2a

[redacted]

Subject Population: Subjects aged 18 years or older, with RRMM and Eastern Cooperative Group (ECOG) performance status of ≤2

Number of Subjects:	**Number of Sites:**
Phase 1: approximately 24 patients. Phase 2a: approximately 18 patients.	Phase 1: approximately 4 investigational centers. Phase 2a: approximately 6 investigational centers.

Dose Level(s):

TAK-079 injections will be escalated as follows: 45 mg, 135 mg, 300 mg, 600 mg, 1200 mg, and 1800 mg in phase 1. After patients have received premedication treatment, doses will be administered with syringes as SC injections up to a maximum of 200 mg TAK-079 in 2 mL per injection. For dose levels where multiple SC injections are needed to administer the full prescribed dose (ie, 300 mg dose and above), the Cycle 1 Day 1 dose will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all drug administration days after Cycle 1 Day 1, if the patient did not have an infusion reaction (IR), the SC injections can be given at the at the same time without a waiting period.

Each dose will be administered as once weekly for 8 weeks (8 doses), then once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks until PD or unacceptable toxicities occur.

For phase 2a, in the absence of DLT, the dose will be selected based upon review of the available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study.

Premedication will be mandatory in phase 1 and phase 2a.

Route of Administration:

Route of administration will be SC.

[redacted]

Duration of Treatment:	**Period of Evaluation:**
TAK-079 will be administered until the patient experiences PD, unacceptable toxicities, or withdrawal due to other reasons. The maximum duration of treatment will be 12 months; however, patients with clinical benefit can continue on treatment beyond 1 year with the explicit approval of the sponsor's study clinician (see Section 6.3).	21 days screening, ongoing treatment to PD. Patients who discontinue treatment for reasons other than PD will continue to be followed for progression-free survival (PFS) every 4 weeks from the end-of-treatment visit until PD, death, the start of subsequent anticancer therapy, study termination, or until 12 months after discontinuation of study treatment, whichever occurs first. Overall survival (OS): Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

Main Criteria for Inclusion:

Male and female patients, aged ≥18 years, with ECOG performance status of ≤2, requiring additional therapy as determined by the investigator. Patients must have received the final dose of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079: 180 days for antibody therapy (including anti-CD38); 90 days for autologous transplantation; 14 days for chemotherapy, radiation therapy, and major surgery; and 7 days for corticosteroid therapy (up to systemic equivalent of 10 mg daily prednisone allowed). Patients must have adequate organ function as determined by the following laboratory values: absolute neutrophil count $\geq 1.0\times10^9$/L; platelets ≥75,000/mm^3 ($\geq 75\times10^9$/L); hemoglobin ≥7.5 g/dL; creatinine clearance ≥30 mL/min (Cockcroft-Gault formula); total bilirubin ≤1.5 times the upper limit of the normal range (ULN); and alanine aminotransferase/aspartate aminotransferase ≤2.5×ULN. Patients must have documented RRMM per the International Myeloma Working Group (IMWG) criteria, with measurable disease defined as one of the following: serum M-protein ≥ 0.5 g/dL (≥5 g/L) and urine M-protein ≥200 mg/24 hours. Patients without measurable M-protein in serum protein electrophoresis or urine protein electrophoresis must have a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal. Patients must have evidence of RRMM as defined by the IMWG criteria, previously received at least 3 lines of myeloma therapy including a proteasome inhibitor (PI), immunomodulatory drug (IMiD), alkylating agent, and steroids. Previous exposure to anti-CD38 as single agent or in combination is allowed but is not mandatory. Patients must be refractory to or intolerant of at least 1 PI and 1 IMiD. Patients who received a combination of PI and IMiD in a unique treatment schedule can be included in the study after at least 2 lines of prior myeloma therapy. Prior treatment with an anti-CD38 monoclonal antibody (mAb) is allowed. In the phase 2a portion of the study, patients must have been refractory to an anti-CD38 mAb therapy at any time during treatment.

Main Criteria for Exclusion:

Sensory or motor neuropathy of Grade ≥3, based on the National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) or not recovered from adverse reactions to prior myeloma treatments/procedures to NCI CTCAE Grade ≤1 or baseline; allogeneic stem cell transplant; congestive heart failure (New York Heart Association) Grade ≥II, cardiac myopathy, active ischemia, clinically significant arrhythmia, history of acute myocardial infarction within 5 months before enrollment, clinically significant uncontrolled hypertension, or any other uncontrolled cardiac condition or concurrent illness that would preclude study conduct and assessment; QT interval corrected by the Fridericia method >480 msec (Grade ≥2); history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-079 formulation (including patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction); history of myelodysplastic syndrome or another malignancy other than MM; clinical signs of central nervous system involvement of MM; or active chronic hepatitis B or C infection, or active HIV infection. Also excluded are patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance; smoldering myeloma; solitary plasmacytoma; amyloidosis; Waldenström macroglobulinemia or immunoglobulin M myeloma, and patients with positive Coombs tests at screening.

Endpoints (in order of importance):

[redacted]

Primary:

Phase 1

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).

Phase 2a

- Overall response rate (ORR), defined as the proportion of patients who achieved a partial response (PR) or better during study as defined by IMWG Uniform Response Criteria.

Secondary:

Phase 1

- RP2D based on both safety and efficacy outcomes
- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079 will be assessed in patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria.
  - Proportion of patients who achieved minimal response (MR), defined as 25% tumor reduction.
- Anti–TAK-079 antibody incidence and characteristics.

Phase 2a

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction, will be evaluated.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the time from the date of the first dose to the date of death due to any cause.
- Time to response, defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

Exploratory:

- [redacted]
- [redacted]

[redacted]

[redacted]

Statistical Considerations:

The MTD/RP2D will be estimated by a 3+3 dose escalation design using data collected in the dose-escalation phase of the study. After review of the available safety, efficacy, PK, [redacted] data, additional cohorts may be expanded by enrolling additional patients to obtain a more comprehensive assessment of disease response and to further inform selection of the R2PD.

Adverse events will be summarized by treatment group and overall. Categorical variables such as ORR will be tabulated by treatment group and overall. Time to event variables such as DOR and PFS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided.

PK parameters will be summarized as appropriate.

Sample Size Justification:

Phase 1 of the study will follow a 3+3 dose escalation schema.

The selection of the next recommended dose will be determined based on safety, clinical, PK, [redacted] data. Dose-escalation cohorts may be expanded to include additional patients to obtain a more comprehensive assessment of disease response before the phase 2a portion of this study is opened to enrollment. Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 24.

In phase 2a, approximately 18 additional patients will be treated to provide a preliminary estimate of the ORR in patients with RRMM. All patients with MM must show clear evidence of PD with anti-CD38 therapy.

Phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

No prospective calculations of statistical power have been made; however, the following table shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this RRMM population.

[redacted]

[redacted]

3.0 STUDY REFERENCE INFORMATION

Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (Appendix C). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

Principal Investigator

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

[redacted]

3.1 List of Abbreviations

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
[redacted]	[redacted]
BMA	bone marrow aspirate
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form (refers to any media used to collect study data [ie, paper or electronic])
EOI	end of infusion
EOT	end of treatment
FDA	United States Food and Drug Administration
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IR	infusion reaction

Abbreviation	Term
IRB	institutional review board
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAB	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PB	plasmablast
PD	progressive disease; disease progression
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS syndrome	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
PR	partial response
QTc	QT interval corrected for heart rate
RBC	red blood cell(s)
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SCRS	severe cytokine release syndrome
SOE	Schedule of Events
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reactions
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration

[redacted]

Abbreviation	Term
[redacted]	[redacted]
TTR	time to response
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WOCBP	women of childbearing potential

4.0 INTRODUCTION

4.1 Background

TAK-079 is a fully human antibody of the immunoglobulin G1 (IgG1) subclass, which targets CD38 expressing cells for destruction through multiple mechanisms of action (complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity). TAK-079 treatment results in a rapid depletion of CD38+ leukocytes in the peripheral blood, as observed in nonhuman primate studies and in humans. A number of hematologic tumors express CD38, including multiple myeloma (MM), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and B-cell non-Hodgkin lymphoma.

MM is a plasma cell-derived malignancy that accounts for approximately 1% of all cancers [1]. It is characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency. The 5-year survival rate of patients with MM is approximately 45% [1]. MM persists as a mostly incurable disease due to its highly complex and diverse cytogenetic and molecular abnormalities [2]. There has been improvement in the outcome for patients with MM in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory drugs (IMiDs) like lenalidomide, but patients who become refractory or are ineligible to receive PIs and IMiDs have a dismal prognosis [3]. In November 2015, the United States Food and Drug Administration (FDA) approved the CD38 antibody daratumumab (DARZALEX; Janssen) for the treatment of MM [4]. Daratumumab was studied in patients who had received at least 3 prior lines of therapy including a PI and an IMiD, or who were double-refractory to these agents. An overall response rate (ORR) of 29% was documented, including a 3% rate of complete response (CR)/stringent complete response (sCR). The main toxicity associated with daratumumab was infusion reactions (IRs), which were severe in some patients. Other common adverse reactions were fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection [5]. Notably, not all patients respond and many patients eventually develop progressive disease on daratumumab monotherapy [6].

4.2 Findings From Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies are provided below. More detailed information is provided in the TAK-079 Investigator's Brochure (IB).

[redacted]

[redacted]

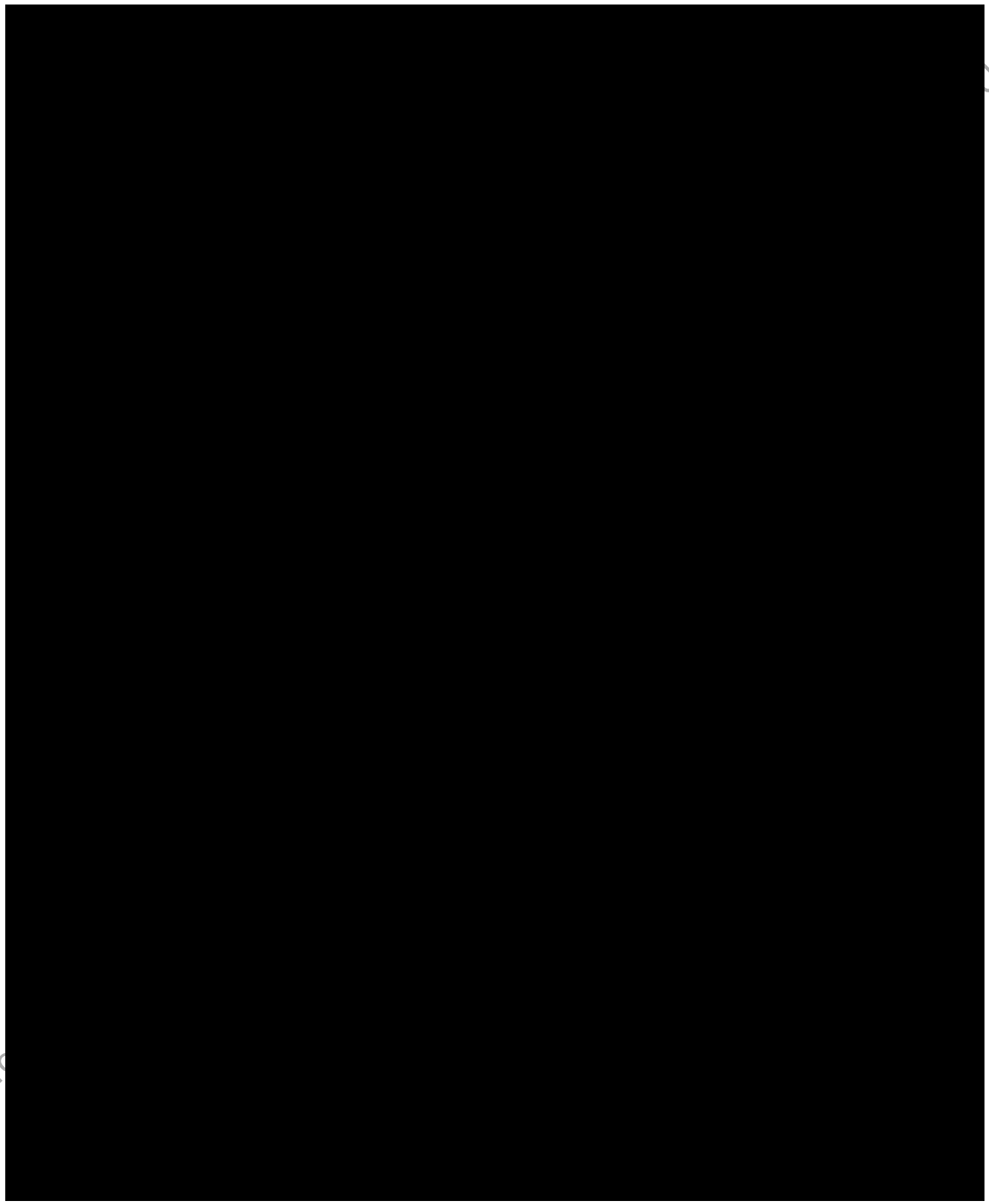
Systemic exposures in the 13-week toxicity studies were considered adequate for assessment despite the formation of antidrug antibodies (ADA) observed more frequently at the lower doses, which negatively affected exposures likely via increased clearance. Assessments of local tolerance via either IV or subcutaneous (SC) dosing routes indicated no significant local injection site liabilities.

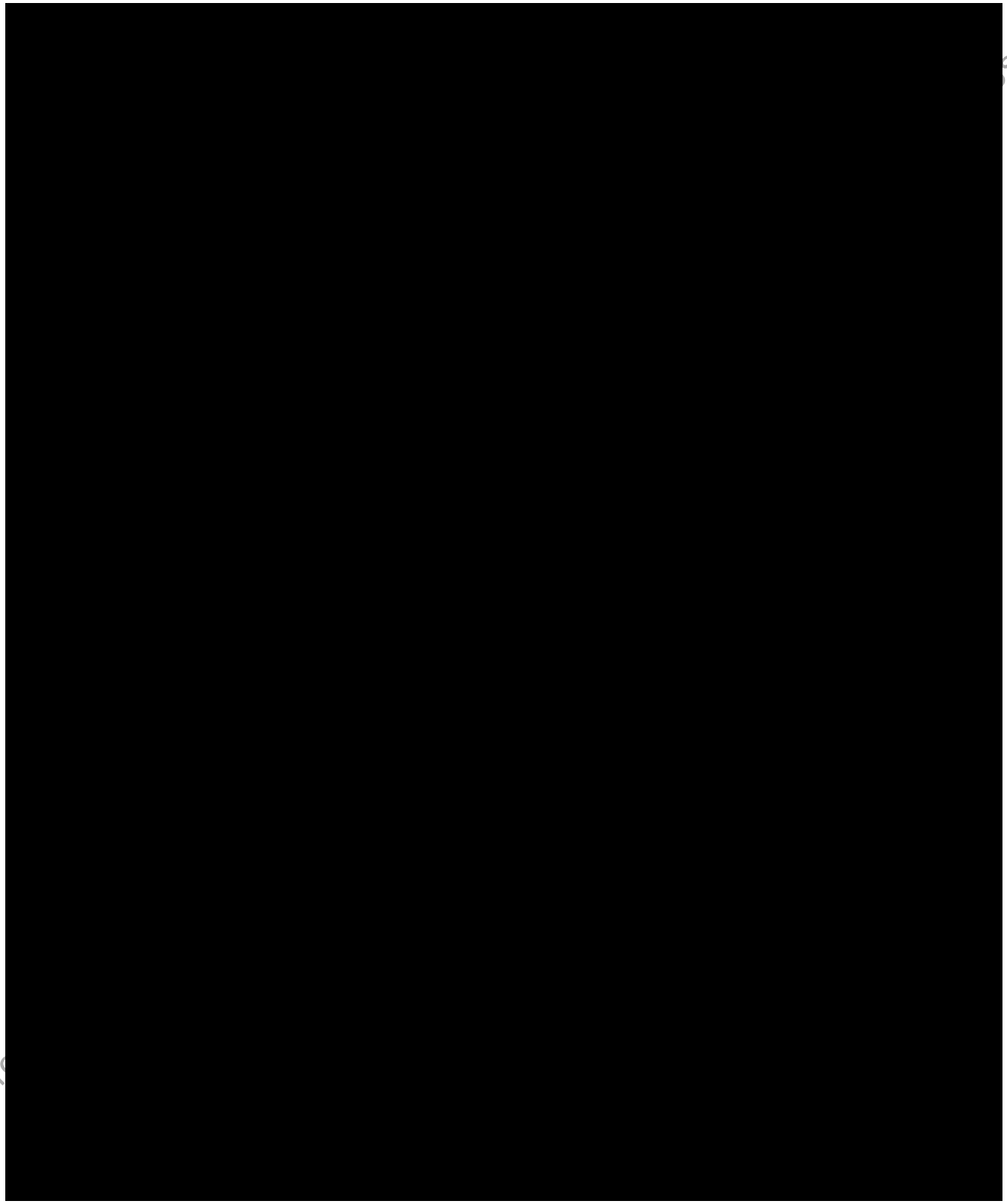
At nontolerated doses in the 4- and 13-week toxicology studies (TAK-079-10001-001A, TAK-079-10015, and TAK 079 10019), some animals developed anemia and thrombocytopenia due to bone marrow hypocellularity affecting all lineages. The mechanism of the marked bone marrow depletion is uncertain. Human erythrocytes [7] and platelets [8] express low levels of CD38, and the presence of erythrophagocytosis in the marrow suggests an immune-mediated component. The absence of erythrophagocytosis in the spleen, lymph nodes, and liver suggests that immune-mediated anemia did not result from targeting of mature erythrocytes. In an investigative study, binding of TAK-079 to cynomolgus or human RBCs or platelets from 30 different donors was not detected; however, a more sensitive assay did subsequently detect binding of TAK-079 to CD38+ expressed on human erythrocytes, which is consistent with binding of daratumumab to human RBCs. A mid-to-low level of CD38+ expression is reportedly present on erythrocytes and megakaryocyte erythroid progenitors. This was confirmed as moderate-to-marked membranous TAK-079 positive staining of hematopoietic cells in human bone marrow, which suggests targeting of progenitor cells as the mechanism of anemia and thrombocytopenia.

Collectively, these data support the continued use of TAK-079 in humans.

4.2.1 [redacted]

[redacted]





4.3 Known and Potential Benefits and Risks to Patients with TAK-079

TAK-079 was administered only in healthy human subjects in the first-in-human (FIH) study (TAK-079_101). Only mild or moderate AEs were observed in the FIH study in healthy subjects. Therefore, clinical benefits and risks have not been assessed in the disease setting.

A summary of findings is discussed in Section 4.3.1. See details for precautions and restrictions in Section 8.7. Additional information regarding potential discomforts and risks from treatment is provided in the TAK-079 IB.

4.3.1 Potential Risks

Based on the mechanism of action of TAK-079, potential AEs may include infusion or injection site reactions, hematological effects, and infections.

4.3.1.1 Infusion and Injection Site Reactions

IRs are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents aimed at treating hematologic malignancies [5]. IRs are less frequently associated with SC injection of these therapies. The 'true' clinical hypersensitivity reactions, antibody-mediated occur after repeat exposure. Symptoms of hypersensitivity range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Non-anaphylactic clinical hypersensitivity occurs within the first hour; however delayed responses were reported. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, bronchospasm, respiratory distress, and shock [9].

There are limited nonclinical and clinical data to date for TAK-079 (Section 4.2.1). Local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. In the clinical study of healthy subjects (TAK-079_101), an infusion-related reaction was defined as a TEAE occurring within 2 hours of the start of an infusion; there were no IRs in this study, as no allergic or cytokine release reactions were observed within this time period. Mild injection site AEs were reported; AEs were Grade 1 and included primarily erythema or tenderness with palpitation. All injection site reactions resolved within a few days.

Patients in clinical trials receiving TAK-079 will be carefully monitored for signs and symptoms of infusion and injection site reactions, with appropriate management of these events. Depending on the severity of the reaction, management may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

See additional details for managing infusion and injection site reactions in Section 8.8.1.

4.3.1.2 Cytokine Release Syndrome

CRS represents an important IR often associated with the use of monoclonal antibodies used in anti-inflammatory and antitumor therapies. CRS may occur early in therapy, and often after the first infusion of the drug due to 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 also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting [10,11].

Severe cytokine release syndrome (SCRS) is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumor lysis syndrome such as hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated lactate dehydrogenase, and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution [10,11]. Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

[redacted]

In the FIH study conducted in healthy human subjects, rarely-observed symptoms consistent with mild CRS were reported particularly at higher doses, and they did not require dose adjustment or interruption. Potential occurrence of events associated with CRS will be carefully monitored in patients receiving TAK-079 and managed according to institutional guidelines. Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

4.3.1.3 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the NOAEL of 0.3 mg/kg.

Subjects in clinical studies of TAK-079 should be monitored closely, including testing of hematology parameters throughout this study, as described in Section 9.4.13 and Appendix A.

4.3.1.4 Infections

In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

[redacted]

Subjects will be monitored for any signs and symptoms of infections throughout this clinical study (see Section 8.8.4).

4.3.1.5 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 monoclonal antibody (mAb), the risk of drug-drug interactions is low.

4.3.1.6 ADA Interactions

ADA responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Strong positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeat-dose toxicity studies and at lower doses.

In the single-dose healthy subject study (TAK-079_101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these, 1 subject was treated in the 0.06 mg IV cohort and the remaining 4 subjects were treated with either 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity.

4.3.1.7 Pregnancy and Lactation

TAK-079 has not been administered to women who are pregnant or lactating. Dedicated fertility and embryo-fetal development toxicology studies have not been conducted with TAK-079. However, there were no TAK-079–related changes in organ weights or microscopic findings noted in the male and female reproductive tract of monkeys following administration for up to 13 weeks. WOCBP may be enrolled in clinical trials with appropriate precautions to prevent pregnancy (additional details in Section 8.7).

At this stage of development TAK-079 should not be administered to women who are pregnant or breastfeeding.

4.3.1.8 Overdose

TAK-079 has been administered only to healthy subjects in the FIH study. To date, there is no experience with overdose. If an overdose does occur, close monitoring and supportive treatment as medically required are recommended.

4.3.2 Overall Benefit and Risk Assessment for This Study

The overall clinical benefits and risks of TAK-079 have not been determined.

Based on the mechanism of action of TAK-079, nonclinical data to date, as well as some exposure in healthy human subjects, possible AEs of TAK-079 include but are not limited to infusion and injection site reactions, CRS, hypersensitivity reactions, changes in hematologic parameters, and infections. Patients will be monitored closely for these risks in this clinical study.

[redacted]

4.4 Rationale for the Proposed Study

Although multiple therapies are available for patients with MM, this disease remains incurable; thus, significant unmet medical need exists for this patient population. Frequent relapses highlight a need for new therapies for patients in whom prior treatments have failed.

TAK-079 binds to unique amino acids of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab.

In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed. For example, NK cells were reduced >90% from baseline levels in all healthy subjects receiving a single 0.06 mg/kg IV dose of TAK-079 and exhibited a mean C_{max} of 0.1 ug/mL (TAK-079_101). Comparable depletion of NK cells by daratumumab administered IV to a population of patients with refractory MM [12] required doses of >24 mg/kg and a mean C_{max} of >500 ug/mL [13,14]. Consequently, TAK-079 may be significantly more efficient at eliminating target cells in patients, which could manifest as higher activity on tumor cells (ie, activity at lower doses, low-volume SC administration, and less frequent administration), including activity on daratumumab-refractory tumors. The potential activity of TAK-079 should therefore be investigated in patients with relapsed and/or refractory multiple myeloma (RRMM).

4.4.1 Rationale for the Starting Dose of TAK-079

In the FIH study (TAK-079_101), TAK-079 was well tolerated after SC administration of single-doses ranging from 0.03 to 0.6 mg/kg.

To avoid unnecessary exposure of patients to sub-therapeutic doses while preserving safety, the starting dose for this study in patients with RRMM will be 45 mg, the fixed-dose equivalent of 0.6 mg/kg (assuming a body weight of 75 kg), which was the highest SC dose administered in Study TAK-079_101. The 0.6 mg/kg dose was well tolerated in healthy human subjects in Study TAK-079_101 and demonstrated >90% depletion of peripheral blood PBs, a surrogate for myeloma cells in each subject (n=6).

TAK-079 is a mAb targeting CD38, which is a cell surface molecule that is constitutively expressed on plasma cells, PBs, and NK cells, and is induced on activated T cells and B cells [15]. Therefore, the anticipated elimination routes for TAK-079 are via proteolytic catabolism and intracellular degradation after binding to its target. Both of these clearance mechanisms are not thought to be significantly influenced by body weight. Additionally, the distribution volume of mAbs is generally limited to the volume of the blood and extracellular fluids, such that body composition is a less important determinant of distribution volume as compared with small molecule drugs [16]. For these reasons, body weight is not expected to have a clinically significant effect on the disposition of TAK-079, thereby supporting the investigation of fixed-dose administration.

The 45 mg starting dose of TAK-079 will be tested in 3 patients with RRMM to assess the safety and tolerability of TAK-079 after multiple dose administration. TAK-079 will be administered using the same dosing schedule as the anti-CD38 antibody, daratumumab, which is approved for

the treatment of patients with MM [5]. Specifically, TAK-079 will be administered once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), then once every 4 weeks until the patient experiences disease progression (PD), unacceptable toxicities, or withdrawal due to other reasons. The subsequent planned dose levels are 135, 300, 600, 1200, and 1800 mg.

Escalation to a subsequent cohort may take place after the treatment in the first cycle of the previous (sequential) cohort has completed.

Additional details for dose escalation are provided in Section 8.3.

[redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

Phase 1

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy in patients with RRMM.

Phase 2a

The primary objective of the phase 2a portion of the study is to provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with RRMM.

5.1.2 Secondary Objectives

Phase 1

The Phase 1 secondary objectives are:

- To investigate a potential MTD/RP2D of TAK-079.
- To evaluate the immunogenicity of TAK-079.
- To characterize the PK of TAK-079.
- To provide a preliminary evaluation of the clinical activity of TAK-079.

Phase 2a

The Phase 2a secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To provide a preliminary evaluation of time-to-event measures.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

5.1.3 Exploratory Objectives

[redacted]

[redacted]

5.2 Endpoints

5.2.1 Phase 1 Primary Endpoints

The primary endpoints for phase 1 are:

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).

5.2.2 Phase 2a Primary Endpoint

The primary endpoint for phase 2a is:

- ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria [17,18].

5.2.3 Phase 1 Secondary Endpoints

The secondary endpoints for phase 1 are:

- RP2D based on both safety and efficacy outcomes.
- Summary statistics for the following PK parameters:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

[redacted]

- Preliminary evaluation of antitumor activity of TAK-079 will be assessed for patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria ([17,18]; Appendix E).
  - Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction ([17,18]; Appendix E).
- Anti–TAK-079 antibody incidence and characteristics.

5.2.4 Phase 2a Secondary Endpoints

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause ([17,18]; Appendix E).
- OS, defined as the time from the date of first dose to the date of death due to any cause.
- Time to response (TTR), defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

5.2.5 Exploratory Endpoints

[redacted]

[redacted]

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients with RRMM, and to provide a preliminary assessment of its activity against MM.

The phase 1 portion of the study will evaluate administration of TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs from medical review of vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, review of concomitant medications, dose modifications, and treatment discontinuations.

The preliminary efficacy of TAK-079 will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [17,18]). In addition, the efficacy of TAK-079 will be assessed by measuring MR, PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the study, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or withdrawal due to other reasons (see Section 6.3).

Phase 1 will consist of the following phases/periods: screening, treatment, and follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing): Once-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.
- Follow-up period (EOT visit): Patients who discontinue study treatment will be followed for approximately 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks from the EOT visit until PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first. Patients who discontinue for PD will be followed for OS after the EOT visit. All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

In phase 1, approximately 6 doses will be evaluated in ascending cohorts of 3-6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

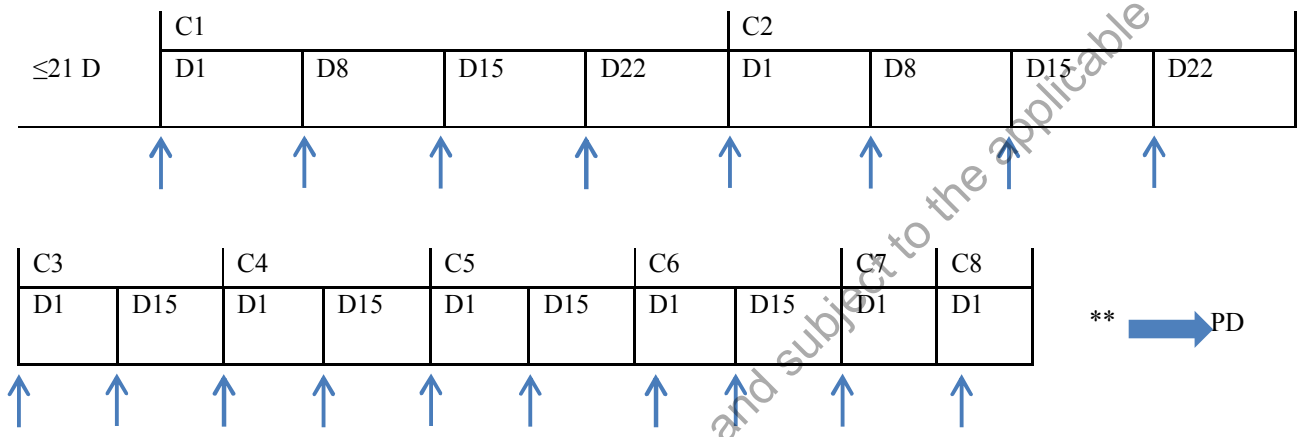
[redacted]

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined.

Study procedures and assessments, with their time points, are shown in Appendix A. The study schematic diagram is shown in Figure 6.a.

Figure 6.a Overall Study Schematic Diagram

Treatment Cycle



C=Cycle; D=Day; PD=progressive disease; R2PD=recommended phase 2 dose; SC=subcutaneous.
Dose Escalation: 45, 135, 300, 600, 1200, and 1800 mg.
Cohorts in phase 1 may be expanded to further inform selection of the RP2D.
The RP2D determined in phase 1 will be further assessed in approximately 18 patients in phase 2a.
* For dose levels where multiple SC injections are needed to administer the full prescribed dose, the Cycle 1 Day 1 dose SC injections will be given with a 30 minute interval in between each SC injection. Thereafter, if there are not clinically significant IRs, the SC injections may be given together without the waiting period.

** → = dosing every 28 days until disease progression.
↑ = TAK-079 dose.

6.2 Number of Patients

For phase 1, approximately 24 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 18 patients are planned. Details on the definition of evaluable patients and sample size are given in Section 13.1.

The study is planned to be conducted in the United States in approximately 4 investigational centers for phase 1 and in a total of 6 investigational centers for phase 2a.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-079 until they experience PD as defined by IMWG criteria [17,18] (Appendix E), unacceptable toxicity, or any other discontinuation criterion is met (see Section 8.4.3 and Section 9.7).The maximum duration of treatment is expected to be 12 months;

however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment beyond 1 year with the explicit approval of the sponsor's study clinician.

Patients will be evaluated 30±7 days after the last dose of TAK-079 (follow-up visit) or before initiating subsequent systemic anticancer therapy, for detection of any delayed TEAEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with TAK-079 plus the EOT visit or after the EOT visit of the last patient entering the study if the sponsor terminates the study early (Table 6.a).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

[redacted]

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint		Definition	Maximum Time Frame From Final Clinical Study Report
Phase 1			
Primary:	Number of patients with TEAEs overall and per dose level: patients with DLTs at each dose level; patients with Grade ≥3 TEAEs; patients with SAEs; patients who discontinue because of TEAEs; patients with dose modifications (delays interruptions, or dose reductions)	Includes assessments for patients with DLTs, Grade ≥3 TEAEs, SAEs, discontinuations because of TEAEs, and dose modifications	1 year
Secondary:	Summary statistics for PK parameters: C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: MR	Proportion of patients who achieved a minimal response, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary:	Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year

ADA=antidrug antibody; C_{max}=maximum observed concentration; DLT=dose-limiting toxicity; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; PK=pharmacokinetics; PR=partial response; SAE=serious adverse event; TEAE=treatment-emergent adverse event; t_{max}=time of first occurrence of maximum observed concentration.

[redacted]

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

Endpoint	Definition	Maximum Time Frame From Final Clinical Study Report
Phase 2a		
Primary: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary: DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification and treatment discontinuation.	Includes assessments for patients with DLTs and other TEAEs, dose modifications and treatment discontinuations.	1 year
Secondary: Summary statistics for PK parameters of C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year
Secondary: Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year
Secondary: MR	Proportion of patients who achieved MR, defined as 25% tumor reduction. See Section 13.1.3.	1 year
Secondary: DOR	Time from the date of the first documentation of response to the date of the first documented PD. See Section 13.1.3.	1 year
Secondary: PFS	Time from the date of the first dose until the earliest date of PD, or the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: OS	Defined as the time from the date of first dose to the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: TTR	Time from the date of the first dose to the date of the first documentation of response (PR or better). See Section 13.1.3.	1 year

DLT=dose-limiting toxicity; DOR=duration of response; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTR=time to response.

[redacted]

6.3.4 Total Study Duration

The final analyses for the clinical study report may be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with TAK-079 or after the last patient completes the EOT visit if the sponsor terminates the study earlier.

It is anticipated that this study will last for approximately 36 months (3 years).

[redacted]

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. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 [19].
3. Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079 (Table 7.a):

Table 7.a Required Washout Periods for Previous Treatments or Procedures Prior to Administration of TAK-079

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	14 days
Antibody therapy (including anti-CD38)	180 days
Corticosteroid therapy (a)	7 days
Autologous transplantation	90 days
Radiation therapy (b)	14 days
Major surgery	14 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.
(b) Prophylactic "spot" radiation for areas of pain is permitted.

4. Patient has adequate organ function as determined by the following laboratory values (Table 7.b):

Table 7.b Laboratory Criteria for Determining Adequate Organ Function for Study TAK-079-1501 Eligibility

Laboratory Parameter	Acceptable Laboratory Criteria
Absolute neutrophil count (a)	≥1000/mm^3 (≥1.0×10^9/L); ≥750/mm^3 (≥0.75×10^9/L) maybe acceptable for patients with >50% of plasma cells in bone marrow after discussion with sponsor
Platelets (a)	≥75,000/mm^3 (≥75×10^9/L); a 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
Hemoglobin	≥7.5 g/dL (it is not permissible to transfuse a subject to reach this level)
Creatinine clearance	≥30 mL/min (Cockcroft-Gault formula)
Total serum bilirubin	≤1.5×ULN; except for patients with Gilbert's syndrome in whom direct bilirubin should be <2.0×ULN
Liver transaminases (ALT/AST)	≤2.5×ULN

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of the normal range.
(a) Without ongoing growth factor or transfusion support for at least 1 week before Day 1.

5. Female patients who:
    - Are WOCBP must not be pregnant or lactating.
    - 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 at least 90 days or 5 half-lives after the last dose of study drug, whichever time period is longest, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
6. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
8. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.
9. Requires additional therapy, as determined by the investigator.
10. Documentation of RRMM as defined by the IMWG criteria (Appendix E; [17,18]).
11. For patients with MM, 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.

[redacted]

- 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.

12. Prior therapy, patients should meet all the following criteria:
    - Patient should be previously treated with at least a PI, an IMiD, an alkylating agent, and a steroid.
    - Patient should be refractory or intolerant to at least 1 PI and at least 1 IMiD.
    - Patient should either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMiD.
    - In phase 1, previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required.
13. In the phase 2a portion of the study, patients with MM must also have been refractory to at least 1 anti-CD38 mAb therapy at any time during treatment.

NOTE:

- Refractory is defined as less than a 25% reduction in M-protein (response of stable disease during prior therapy) or PD during treatment or within 60 days after last dose of prior therapy.
- A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of PD, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease [17].

7.2 Exclusion Criteria

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

1. Sensory or motor neuropathy of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 [20].
2. Patients who have received allogeneic stem cell transplant.
3. Patients who have received anti-CD38 antibody therapy and do not fulfill a 180-day washout period before receiving TAK-079.
4. Not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE Grade ≤1 or baseline, excluding alopecia.
5. Congestive heart failure (New York Heart Association) Grade ≥II; cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically

significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.

6. History of acute myocardial infarction within 5 months before enrollment or ECG abnormalities during the screening period that are deemed medically relevant by the investigator.
7. QT interval corrected by the Fridericia method >480 msec (Grade ≥2).
8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume <80%, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.
9. History of stroke or intracranial hemorrhage within 12 months of first dose of study drug; patients requiring anticoagulation therapy for any indication should be discussed with the medical monitor before screening.
10. Active autoimmune disease including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or any chronic condition requiring a higher corticosteroid systemic equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped 7 days prior to first dose of study drug; exceptions may be made for corticosteroids prescribed specifically for management of MM symptoms after discussion with the medical monitor.
11. History of myelodysplastic syndrome or another malignancy other than MM, except for the following: any malignancy that has been in complete remission for 3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, or asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year before the start of study therapy.
12. Clinical signs of CNS involvement of MM.
13. Female patients who are pregnant with a positive serum pregnancy test or lactating during the screening period, or a positive urine pregnancy test on Day 1 before the first dose of study drug, if applicable.
14. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or active HIV infection.

[redacted]

16. History of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation. This includes patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction.
17. The patient is currently participating in another antimyeloma clinical study, or has participated in another investigational clinical trial within the 4 weeks prior to first dose of study drug.
18. Patients who are not able and/or willing to comply with the study requirements, rules, and procedures.
19. POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, or IgM myeloma.
20. Patients with positive Coombs tests at screening.

[redacted]

8.0 STUDY DRUG

8.1 Study Drug Administration

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

8.1.1 Predose and Postdose Medication

Predose Medication

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor).

NOTE: For any patients with a history of COPD, consider prescribing postinfusion medications such as short- and long-acting bronchodilators, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional inhaled postinfusion medications may be discontinued.

Premedications are required in phase 1 and phase 2a.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

Postdose Medications

Postinjection site care: Apply 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).

Patients may receive low-dose methylprednisolone (< 20 mg) for the prevention of delayed injection-related reaction as clinically indicated after an injection.

8.1.2 TAK-079 Formulation and Administration

The strength of the TAK-079 drug product for SC use in the current study (TAK-079-1501) is 100 mg TAK-079 in 1 mL (100 mg/mL). The drug product is supplied in clear borosilicate glass vials (see additional details in Section 8.10).

After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL). For dose levels where multiple SC injections are needed to administer the full prescribed dose (ie, 300 mg dose and above), the Cycle 1 Day 1 dose will be administered by giving each SC injection 30

minutes apart until the full scheduled dose has been administered. On all drug administration days after Cycle 1 Day 1, if the patient did not have a clinically significant IR per the investigator, the SC injections can be given at the at the same time without a waiting period.

When patients are to receive multiple SC injections, 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.

Refer to the Pharmacy Manual for detailed instructions regarding preparation of each dose.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [20]. These criteria are provided in the Study Manual. DLTs will be defined as any of the following events regardless of relationship, except those events that are clearly due to extraneous causes.

- Grade 4 laboratory abnormalities, except those events that are clearly due to extraneous causes, will be defined as a DLT.
- Nonhematologic TEAEs of NCI CTCAE Grade ≥3, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - Grade 3 nausea/vomiting that can be managed subsequently with antiemetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 3 days (approximately 72 hours).
  - Grade 3 elevation of alanine aminotransferase or aspartate aminotransferase that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms. See Section 8.8.1 for handling of IRs with systemic signs and symptoms.
- Hematologic TEAEs of NCI CTCAE Grade ≥4, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis, except those events that are clearly due to extraneous causes (eg, negative direct Coombs test), will be included in the definition of DLT.
  - Grade ≥3 low platelet count with clinically meaningful bleeding, defined as a blood loss of >100 cc or the requirement of a blood transfusion, will be included in the definition of DLT.

- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a DLT.

For the purpose of dose escalation, DLTs are those events meeting the criteria above that occur before Cycle 2 Day 1 administration. TEAEs meeting DLT definitions occurring in later cycles will determine the suitability of the MTD as the RP2D.

Patients who experience a DLT should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort; such patients will not count as a patient in that lower dose cohort for escalation decisions.

In phase 1, patients who do not receive 4 full doses of TAK-079 within the 28-day (±2) treatment window or the Day 29 (ie, Cycle 2 Day 1) assessment for reasons other than a DLT will be replaced. Patients experiencing a DLT should not be replaced.

Dose and schedule modifications for toxicity are described in Section 8.4.

8.3 Dose-Escalation Design and Criteria

8.3.1 Dose Levels

Patients will be enrolled in cohorts of 3 to 6, following a 3+3 dose escalation design.

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 300 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 600 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

[redacted]

Cohorts may be expanded by enrolling additional patients to obtain more comprehensive assessment of disease response and to further inform selection of the RP2D.

[redacted]

Phase 2a

In the absence of DLT, the dose that will be administered in the subsequent phase 2a portion of the study will be based upon a comprehensive review of available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study. Also note Section 13.1.7 for phase 2a safety review.

8.3.2 Escalation Schema

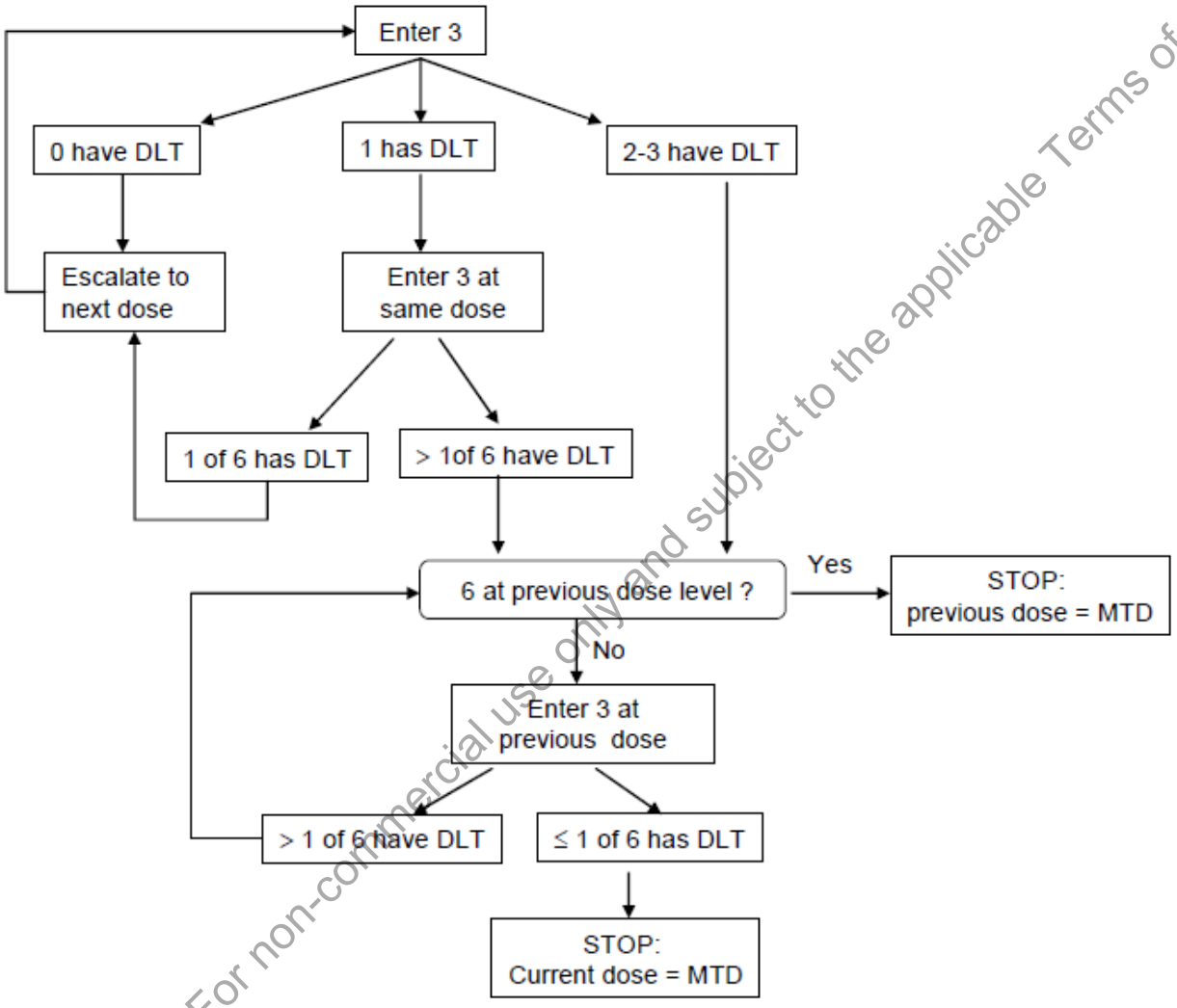
A 3+3 dose escalation schema will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
- If ≤1 of 6 patients experiences a DLT, escalation will continue to the next higher dose level, at which 3 patients will be enrolled.
- If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3 patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and this dose level may be considered the MTD. The MTD is defined as the highest dose with a cohort of 6 patients having no more than 1 patient with a DLT.

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm.

[redacted]

Figure 8.a Dose-Escalation Scheme



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

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, [redacted].

Before initiating the dosing of the next cohort, when safety data are available for all patients in the current cohort, key safety data will be reviewed and evaluated by the study team consisting of sponsor representatives and investigators who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, changes to the dose-escalation scheme or dose schedule (dosing interval) may be considered. All decisions will be documented in writing. Any decision to modify the dose-escalation scheme (with the exception of testing intermediate

[redacted]

dose levels) or dose schedule will be communicated to institutional review boards (IRBs), and the protocol will be amended accordingly.

8.4 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for TAK-079 on the basis of the type and severity of AEs and causality determination by investigators (see Section 8.4.2). Further clarification can be obtained in consultation with the sponsor clinician (or designee).

8.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with TAK-079 will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- Absolute neutrophil count must be $\geq 1000/mm^3$.
- Platelet count must be $\geq 75{,}000/mm^3$.
- For therapy to resume, toxicity considered to be related to treatment with TAK-079 must have resolved to Grade ≤1 or baseline, or to a level considered acceptable by the physician. If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If there is a delay of a subsequent cycle longer than 28 days because of a drug-related AE, 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.
- For TAK-079 injections within the same cycle, the decision of holding treatment is left to the investigator's discretion based on clinical and analytical data, and also based on the toxicity that the patient experienced with previous injections in the same cycle. The investigator should differentiate between acute toxicity (like an IR) from which the patient is recovered at the time of the next injection, and subacute toxicity (for example, neutropenia) that might be worsened upon another injection if it is not on a clear recovery path. If the dose cannot be administered on the scheduled day, the patient can be reviewed at the investigator's discretion in the following 48 hours. If TAK-079 cannot be administered within a cycle in this 48-hour window, the dose will be missed and the patient scheduled for the next administration per the Schedule of Events (SOE; Appendix A).

8.4.2 Criteria for Dose Modification

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 TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, depending on the nature and severity of the AE and whether it is the first occurrence or it is recurrent.

[redacted]

TEAEs that are not attributed by the investigator to the study drug 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 TAK-079.

Table 8.a provides general dose modification recommendations. When the dose of TAK-079 is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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 monoclonal antibodies as a means to reduce dose intensity [5,21,22]. Patients experiencing a DLT (defined in Section 8.2) should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort.

See details for managing specific AEs in Section 8.8.

[redacted]

Table 8.a Dose Modification Recommendations for TAK-079 Toxicities

Criteria	Action
Grade 1 AEs	No dose interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same dose is 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. (Note Section 8.2 for AEs of short duration and/or that respond to medical management.) Note in phase 1, nonhematologic AEs Grade ≥3 may meet DLT criteria and as such patients should be withdrawn from further dosing unless the sponsor approves subsequent treatment in a lower dose cohort. Grade 3 or higher thrombocytopenia with bleeding should result in a dose interruption until the AE resolves to Grade ≤1 or baseline, then resume at the same dose. Medical considerations should eliminate Coombs positivity before restarting (note Table 8.b).
Grade 4 (life-threatening) AEs	Patients with Grade 4 AEs 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. Medical consideration should eliminate Coombs positivity before restarting (note Section 8.4.3 and Table 8.b).
AEs of all grades	If TAK-079 administration does not commence within the prespecified window (Table 8.b) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date upon recovery as described above.

AE=adverse event; DLT=dose-limiting toxicity.

If initial dose interruption does not provide sufficient relief, the dose of TAK-079 should be considered for permanent discontinuation.

Table 8.b TAK-079–Related Toxicity Management

Dosing Frequency	Dose Missed	Dosing Resumption
Weekly (QW)	>3 days	Skip dose, move to next planned weekly dosing date
Biweekly (Q2W)	>7 days	Skip dose, move to next planned biweekly dosing date
Every 4 weeks (Q4W)	>21 days	Skip dose, move to next planned every 4 weeks dosing date

A TAK-079 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

[redacted]

possible. Subjects missing ≥3 consecutive planned doses of TAK-079 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 TAK-079 during every-4-weeks dosing may be delayed (interrupted) up to 4 weeks. 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 TAK-079 that requires a dose delay (interruption) of more than 28 days should result in permanent discontinuation of TAK-079, unless both the investigator and the sponsor study clinician believe the patient is deriving clinical benefit.

8.4.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification)

TAK-079 should be discontinued in patients experiencing an AE in Cycle 1 that meets the criteria for a DLT, unless the investigator considers that re-treatment of the patient not to be dangerous and the sponsor approves subsequent treatment in a lower dose cohort. For Grade 4 (life-threatening) TEAEs, consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit, there are opportunities to provide supportive care to mitigate risk for the Grade 4 event to reoccur, and this approach (ie, the specific situation and mitigation plan) has been discussed with the sponsor. In these circumstances, treatment may be restarted when toxicity recovers to Grade ≤1 or baseline (see Table 8.a and Table 8.b).

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy and radiation therapy for the disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor's medical monitor and once PD is ruled out.
- Systemic corticosteroid use >10 mg/day (prednisone or equivalent).
- Live vaccines.
- Any investigational agent other than TAK-079, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.

8.6 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 received until 30 days after the final dose will be recorded in the electronic case report forms (eCRFs) (note additional information in Section 9.4.9 and Appendix A).
- The following medications and procedures are permitted while the patient is receiving the study drug:
  - Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent).

- Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice.
- Transfusions with RBCs and platelets as clinically indicated; localized radiation for pain management for osteolytic lesions.
- Concomitant treatment with bisphosphonates will be encouraged for all 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. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.
- Topical or inhaled steroids and short-acting β_2 adrenergic receptor agonists (eg, for the treatment of asthma) are permitted.
- Nonresorbable corticosteroids (eg, budesonide).
- Plasmapheresis.

8.7 Precautions and Restrictions

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

NSAIDs should be avoided with impaired renal function given the reported NSAID-induced renal failure in patients with decreased renal function.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-079 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following:

- WOCBP must not be pregnant or lactating.
- 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 at least 90 days or 5 half-lives after the last dose of study drug (whichever is longer), OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and 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 one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium, and uric acid levels must be performed. Patients with tumor lysis syndrome should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis as indicated).

8.8 Management of Specific Adverse Reactions

8.8.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any systemic IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of an IR (any grade), blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

For additional details, refer to Section 9.4.15.3.

Grade 1 or 2 IR

In case of Grade 1 or 2 IRs (systemic signs or symptoms):

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.

- If a patient experiences a Grade 1 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once the patient is stable per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.
- If a patient experiences a Grade 2 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once resolved to Grade 1 or resolved completely, per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.

– Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. Subsequent doses may have individual SC injections administered more frequently at the investigator's discretion with appropriate premedication and postmedication.

Grade 3 IR

In case of Grade 3 IRs (systemic signs or symptoms):

- Withhold therapy (also administration of remaining SC injections if full dose was not yet reached and therefore skip remaining injection[s]) until next scheduled TAK-079 SC administration, providing that the IR has recovered to Grade ≤1 at the time of the next scheduled TAK-079 dose. Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. At the time of the next dose after an IR, patients at a dose level requiring more than 1 SC injection should receive each injection 30 minutes apart. If no further IR, subsequent injections may be given more frequently at the investigator's discretion with appropriate premedication and postmedication.
- Permanently discontinue treatment after the third occurrence of Grade 3 IRs.

Grade 4 IRs

In case of Grade 4 IRs (systemic signs or symptoms):

- Permanently discontinue treatment.

8.8.2 Injection Site Care

Prophylactic postinjection site care:

- Apply 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).

[redacted]

8.8.3 Handling of Low Platelet Counts

Treatment decisions will be based on patient platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled treatment to be postponed or to be permanently discontinued if recovery is delayed more than 14 days (see Table 8.a). If at any time the platelet count is less than 10×10^9/L, or if the patient shows a bleeding tendency considered to be due to thrombocytopenia occurring after initiation of TAK-079 treatment, the patient should be withdrawn from TAK-079 treatment. Platelet transfusion and daily monitoring of platelet counts, evaluation of coagulation parameters, and the Coombs test are recommended. These patients (that is, those who have platelets $<10\times10^9$/L if recovery is delayed more than 14 days OR with bleeding tendency due to thrombocytopenia OR with abnormal Coombs test) should be considered as having experienced an SAE.

8.8.4 Risk of Infection

The intended mechanism of action of TAK-079 may involve reduction of the subject's immune response. Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis treatment (eg, antiviral medication) may be initiated as clinically indicated, as determined by the investigator. Patients during the study should be followed closely for signs and symptoms of infection and treated as clinically indicated.

Until more clinical experience is gained with the use of TAK-079, it is prudent to avoid situations that may place subjects at increased risk of infection.

8.8.5 Transfusion Risks

Blood samples from patients being treated with TAK-079 may show pan reactivity during pretransfusion testing. To facilitate the provision of blood components for such patients, it is recommended that a baseline phenotype or genotype be established before starting treatment with TAK-079. Patients should keep this information in case future transfusions are needed. If a patient requires RBC phenotyping after the start of TAK-079 treatment, dithiothreitol treatment of the patient's RBCs should be performed, in case of preexisting positivity to standard tests.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

[redacted]

[redacted]

8.11 Preparation, Reconstitution, and Dispensation

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

TAK-079 is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling TAK-079.

8.12 Packaging and Labeling

Supplies of TAK-079 will be labeled according to the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

8.13 Storage, Handling, and Accountability

8.13.1 Storage and Handling

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label (see the Pharmacy Manual for additional information).

During shipping, vials will be protected from light and maintained below -15°C (5°F). Each TAK-079 shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

[redacted]

The investigator is responsible for ensuring that deliveries of TAK-079 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Detailed dosage preparation instructions are provided in the Directions for Use section of the Pharmacy Manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the Pharmacy Manual.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the Pharmacy Manual.

8.13.2. Accountability and Destruction of Sponsor Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator must maintain 100% accountability for all study medication (TAK-079) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- Per standard clinical practice, a site representative, otherwise uninvolved with study conduct, will review the subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication. This review will be documented at the site.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Empty, partially used, and unused TAK-079 will be disposed of, retained, or returned to the sponsor or designee, as directed by the sponsor or designee.

The investigator must maintain a current inventory (Drug Accountability Log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and subjects' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

8.14 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned using an 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 numbers (MED IDs) 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.

[redacted]

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, any clinical laboratories centrally analyzing samples, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC). The screening period for this study is 21 days.

9.3 Treatment Group Assignments

All patients will receive open-label treatment with TAK-079 as indicated in respectively assigned treatment cohorts.

9.4 Study Procedures

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. This includes initial diagnosis date and MM staging at initial diagnosis using the International Staging System and Salmon-Durie Staging. Before dosing, the investigator should record the International Staging System as of study entry, which should be consistently used throughout the study.

Known cytogenetic alterations should also be collected. Prior treatment regimens, with each treatment duration (start and stop dates), the best response obtained with each therapy, and date/type of disease progression should be recorded. Refractoriness to previous treatments should be collected following IMWG criteria (Appendix E). Confirm that the patient's current medical status does not include active chronic HBV, HCV, or HIV infection.

[redacted]

For patients who have received previous anti-CD38 therapy, the worst grade of infusion-related reactions should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

Information on any subsequent anticancer therapies will be collected during the PFS/OS follow-up periods.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured during the screening visit only. Weight will be measured on Day 1 of each treatment cycle, as indicated in Appendix A.

9.4.6 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital sign measurements will be made before TAK-079 injection and include supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position). All measurements should be performed in the same initial position, including heart rate and body temperature.

Blood pressure will also be measured before each injection, and at any time the patient complains of symptoms consistent with IR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Vital signs will be measured at the visits specified in the SOE (Appendix A). 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 10.2.

9.4.7 Eligibility Criteria

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.

9.4.8 Pregnancy Test

WOCBP must have 2 negative pregnancy tests (human chorionic gonadotropin <5 mIU/mL) prior to starting study drug. A serum pregnancy test will be used during the screening period (within 10 to 14 days before the start of study drug). A serum pregnancy test must also be performed at baseline (within 24 hours before the start of study drug). A WOCPB is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential)

for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

During the study, if a menstrual period is delayed, absence of pregnancy in WOCBP must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study upon request by an IRB or if required by local regulations.

A urine pregnancy test is required in WOCBP at designated treatment visits (Appendix A) and also at the EOT visit.

9.4.9 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had within 21 days before TAK-079 administration and up to 30 days after the last dose of TAK-079 (or the start of subsequent anticancer therapy, whichever occurs first) will be recorded on the eCRF. Trade name and international nonproprietary name/generic name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF. See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.10 AEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.4.11 Enrollment

A patient is considered to be enrolled in the study at the first injection.

Procedures for completing the enrollment information are described in the Study Manual.

9.4.12 ECG

A single ECG will be collected at the screening visit for assessment of eligibility. A qualified person will interpret the ECG.

Time-matched triplicate 12-lead ECGs and PK samples will be collected in this study during Cycles 1 and 2 as specified in Appendix B. Although the number of scheduled ECG measurements will not be increased, the timing may be changed if emerging data indicate that an alteration in the ECG schedule is needed. Triplicate ECGs will be recorded electronically and transmitted to a central vendor for storage.

The triplicate ECG measurements should be completed before the PK blood draw. Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement.

[redacted]

Single, 12-lead ECGs will be administered at all other designated visits (ie, after Cycle 2), as specified in Appendix A.

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally (includes the direct and indirect Coombs tests). Exceptions are discussed below.

Handling of clinical laboratory samples will be outlined in the Study Manual. The [redacted], PK, and immunogenicity (ADA and potential neutralizing antibodies [NAB]) assessments are to be performed centrally.

CD38 expression of MM cells will be assessed by multicolor flow cytometry; analysis will be done centrally. [redacted]

Decisions regarding eligibility for this study may be made using local laboratory determinations in the dose-escalation portion of phase 1 of this study. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

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

[redacted]

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
ANC	Albumin	Creatinine clearance
Hematocrit	ALP	CRP
Hemoglobin	ALT	Glucose (nonfasting)
Platelet (count)	AST	GGT
Reticulocyte count	Bilirubin (total)	LDH
RBC count	BUN	Phosphate
WBC count	Calcium	Potassium
WBC with differential	Chloride	Sodium
Coagulation panel	CO_2 (bicarbonate)	Total protein
	Creatinine	Urate (uric acid)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=serine aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=γ-glutamyl transferase; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell.

Table 9.b Clinical Urinalysis Tests

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

For estimation of creatinine clearance, the Cockcroft-Gault formula will be employed as follows:

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

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

9.4.13.2 Prestudy Prognostic Risk Assessment

A blood sample will be collected for serum β_2 microglobulin at screening to assess patient disease status. Results will be analyzed locally.

9.4.14 Disease Response Assessments

Patients will be assessed for disease response according to the IMWG criteria ([17,18]; Appendix E).

Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079. Patients measurable by

SPEP only will have 24-hour urine collected at screening and EOT and to document PR, very good partial response (VGPR), CR, or PD.

Imaging tests will be done per Appendix A and as described in Section 9.4.14.1. The same imaging technique should be used throughout the study to facilitate consistent disease assessment.

Responses should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.

Note that to determine a response of sCR, BMA immunohistochemistry or immunofluorescence for kappa:lambda ratio, as well as serum FLC assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

PD may be confirmed per standard clinical practice at the site. Local laboratory results may be used to confirm PD.

Blood samples, 24-hour urine sample, BMA, and imaging done for disease response assessment will be done locally.

9.4.14.1 Computed Tomography/Magnetic Resonance Imaging

Scans will be performed at a minimum at screening and at the EOT visit. All treatment phase and follow-up scans should use the same imaging modality used at screening.

For patients with documented extramedullary disease, a whole-body x-ray, positron emission tomography-computed tomography (PET-CT) scan, computed tomography (CT) scan (includes low-dose CT), or magnetic resonance imaging (MRI) scan will be performed as outlined in Appendix A. The screening scan may be performed up to 21 days before first dose of TAK-079; however, if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, that image can be used as baseline and does not need to be repeated as part of screening. If disease is documented, then a repeat PET-CT scan, CT scan, or MRI scan should be performed as required to document response or PD.

Additional surveys (x-ray, CT, or MRI) may also be performed at the investigator's discretion, eg, in case of bone pain. Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.4.14.2 Quantification of Immunoglobulins

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained at the screening visit, predose on Day 1 of every cycle, and at all visits per Appendix A. Analysis of Ig will be performed locally.

9.4.14.3 Quantification of M-Protein

A predose blood and 24-hour urine sample will be obtained at the screening visit, Day 1 of every cycle, and at all visits per Appendix A.

The samples will be tested locally. M-protein in serum and urine will be quantified by SPEP and UPEP.

9.4.14.4 Serum FLC Assay

Serum samples will be obtained predose on Day 1 of every cycle and at all visits, per Appendix A, for the serum FLC assay (including quantification of kappa and lambda chains and ratio). Blood samples will be analyzed locally.

9.4.14.5 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, to confirm CR, and at all response assessment visits as per Appendix A. Immunofixation testing will be performed in a local laboratory.

9.4.14.6 BMAs

Central Laboratory Evaluations

BMAs will be taken during the screening period and at the beginning of designated study visits at Cycles 2, 4, 7, and at Cycle 13, with some aspirate samples sent for central analysis (note Table 9.c).

Local Laboratory Evaluations

Disease Assessment

A BMA will be obtained at screening for disease assessment (if a standard BMA was drawn within 5 weeks before consent, that BMA can be used as baseline and does not need to be repeated as part of screening unless cytogenetic evaluation is not available). A BMA will also be obtained at any time to assess CR or as needed to investigate suspected PD. Requirements for BMA assessments to confirm disease responses are defined above and will be analyzed locally (see Section 9.4.14).

Cytogenetics

Patients who do not have historically documented cytogenetic results for the high-risk abnormalities of del (17), t(4:14), and t(14:16) will have cytogenetic evaluation performed on the BMA sample at screening. Cytogenetic evaluation may be performed using fluorescence in situ hybridization or conventional cytogenetics (karyotype). At a minimum, cytogenetic markers must include the 3 high-risk abnormalities of del(17), t(4:14), and t(14:16). Additional abnormalities (amp1q, del13, or del1p) may also be tested. Cytogenetics will be analyzed locally, according to local standards.

[redacted]

9.4.15 [redacted], PK, [redacted], and Immunogenicity Samples

9.4.15.1 Primary Specimen Collection for PK, [redacted], and [redacted] Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix B for the measurement of serum concentrations of TAK-079 and in Appendix A for [redacted].

The primary specimen collection is presented in Table 9.c. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.c Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for TAK-079 PK	Serum	PK measurements	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
Serum sample for immunogenicity	Serum	Immunogenicity assessments	Mandatory
Serum sample for direct and indirect Coombs test	Serum	Immunogenicity assessments	Mandatory

PK=pharmacokinetics.

9.4.15.2 PK Measurements

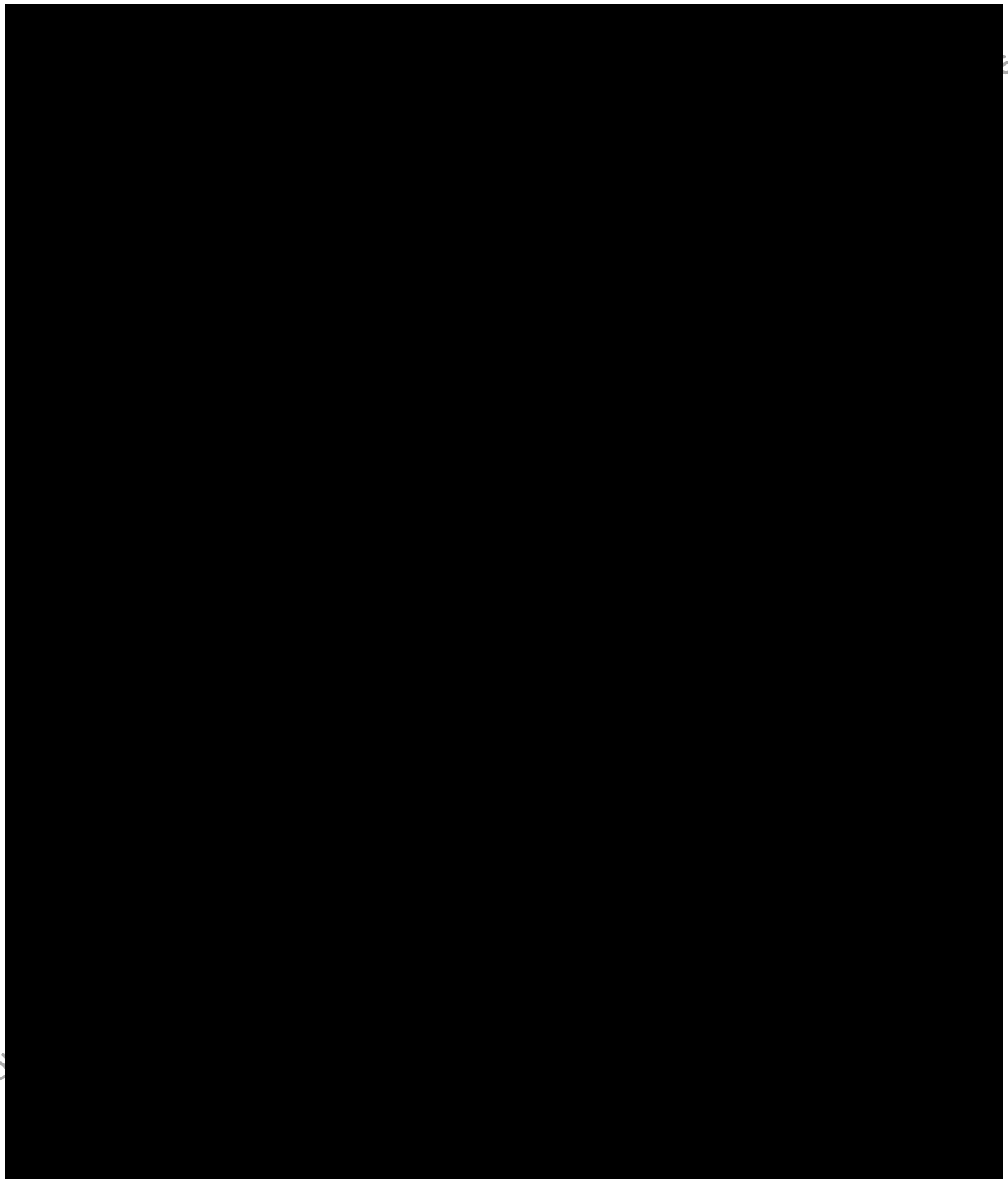
Serum samples for the measurement of concentrations of TAK-079 will be collected at multiple time points as specified in Appendix B.

The timing, but not the total number, of samples may be modified during the study on the basis of emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual.

9.4.15.3 [redacted]

[redacted]



[redacted]

9.4.15.4 Immunogenicity Assessments

ADA Assessment

Serum samples for the assessment of anti–TAK-079 immunogenicity will be collected at the study visits specified in Appendix A. A blood sample will be collected before administration of TAK-079 (ie, prior to dosing on Day 1; baseline value) then subsequently before TAK-079 dosing at each designated visit (postbaseline values), and at visits for any patient who experiences a TEAE considered by the investigator to be consistent with hypersensitivity/IR.

A sample will initially be screened for ADA titer. If a sample is detected as ADA positive, it may be assessed for neutralizing activity.

Direct and Indirect Coombs Testing

Serum samples for direct and indirect Coombs testing will be collected at time points specified in Appendix A. These tests will be performed locally.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered as having completed study treatment if they discontinued study drug for any reason as outlined below in Section 9.7.

9.6 Completion of Study (for Individual Patients)

Patients will receive TAK-079 until they experience PD, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor (see additional details in Section 9.8).

Patients will have a follow-up visit 30 days after the last dose of study drug or prior to the start of subsequent alternative anticancer therapy, to permit the detection of any delayed AEs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, the start of subsequent anticancer therapy, study termination, or until 12 months after discontinuation of study treatment, whichever occurs first.

[redacted]

Patients will be followed every 12 weeks for OS until death, loss to follow-up, consent withdrawal, or study termination.

It is anticipated that the duration of the study will be approximately 36 months (3 years).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.
- Withdrawal by patient.
- Female patient has confirmed pregnancy.

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

- AE/SAE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.
- Other.

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

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

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 by patient (mandatory immediate discontinuation of study agent).
- Death.
- PD.

- Other.

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

9.9 Study Compliance

Study drug will be administered 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 stop treatment for any reason other than progressive disease will continue to have progression-free follow-up visits (additional details in Section 9.6). Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first.

Patients who stop treatment due to PD will continue to have OS visits. Patients will be followed every 12 weeks for OS after documented PD until death, loss to follow-up, consent withdrawal, or study termination.

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.

See the SOE (Appendix A) for appropriate assessments during follow-up.

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

[redacted]

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 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 4.03, effective date 14 June 2010 [20]. 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 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 <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 and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

Cognizant
United States and Canada
Toll-free fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

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

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

pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [20]. 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 next-line subsequent anticancer therapy, or 6 months after PD has occurred, whichever comes first.

SAEs:

- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 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 caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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

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

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

Product	Call Center	Phone Number	E-mail	Fax
TAK-079	DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2)

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

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

[redacted]

11.0 STUDY-SPECIFIC COMMITTEES

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

[redacted]

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of

a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

[redacted]

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of TAK-079.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-079 and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of TAK-079.

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, and DOR.

[redacted]

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient dosing data and TAK-079 concentration-time data to permit the calculation of PK parameters.

Immunogenicity analysis set: The immunogenicity analysis set will include those patients from the safety population who have baseline and at least one postbaseline sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. 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 if necessary.

[redacted]

13.1.3 Efficacy Analysis

Data from any efficacy assessments performed after the specified follow-up time will not be collected on the eCRF; if such data are collected, these data will not be analyzed.

The preliminary efficacy of TAK-079 for MM will be evaluated by measuring the ORR defined as the proportion of patients who achieved a PR or better during study; the composition of sCR, CR, VGPR, and PR as defined by the IMWG Uniform Response Criteria (see Appendix E).

In addition, the efficacy of TAK-079 will be assessed in patients by measuring DOR, PFS, and 1-year OS. TTR will also be measured.

13.1.4 PK Analysis

PK parameters will be estimated using noncompartmental analysis methods. Parameters will be calculated for individual patients included in the PK analysis set using the TAK-079 concentration-time data. The calculated PK parameters will include, but not be limited to, C_{max}, t_{max}, and AUC_{last} (as permitted by the data).

PK parameters will be summarized using descriptive statistics. Individual TAK-079 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 PK data collected in this study may also contribute to future population PK analyses of TAK-079. These population PK analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Similarly, the time-matched PK and triplicate ECG data collected in this study may contribute to future concentration-QT interval corrected for heart rate (QTc) analyses. These analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the concentration-QTc analysis will be separately defined, and the results will be reported separately.

13.1.5 [redacted]

[redacted]

13.1.6 Immunogenicity Analyses

TAK-079 immunogenicity will be analyzed using the immunogenicity analysis set. The proportion of patients with positive ADA (transient and persistent) will be summarized, and the proportion of patients in phase 2a with positive neutralizing ADA during the study may be

[redacted]

summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined. NABs may also be assessed in patients.

The immunogenicity of TAK-079 will be assessed by determining anti–TAK-079 antibody incidence and characteristics (eg, titer, transiently, and persistently ADA; and possible neutralizing activity). Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-079 antibodies on the PK profile, drug efficacy, and clinical safety will be evaluated, if possible.

13.1.7 Safety Analysis

The safety and tolerability of TAK-079 will be assessed by the recording and analysis of TEAEs (NCI CTCAE version 4.03; [20]), vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, and concomitant medications.

TEAEs will be summarized using the safety analysis set and will be coded using the MedDRA. Data will be summarized using preferred term and primary system organ class.

In the phase 2a portion of this study, Grade 4 or higher nonhematological toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients. If the stopping bounds of ≥4/10 and ≥6/20 have been reached, accrual to the study will be suspended to allow for investigation. After consideration by the study team, a decision will be made as to whether accrual can be resumed. The bounds 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 18% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate [23].

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately 18 patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with RRMM.

A 3+3 dose escalation schema will be used for dose escalation as described in Section 8.3.2.

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile.

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and [redacted] before the phase 2a of this study is opened to enrollment. Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 24.

[redacted]

In phase 2a, up to a total of 18 patients will be treated to provide a preliminary estimate of the ORR in patients with RRMM. All patients must show a clear evidence of PD with anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 13.a shows the width of the 80% CI, based on the observed ORR in a cohort size of 18 patients, for a range of observed response rates. An observed ORR greater than 20% would be of interest in this relapse/refractory population.

Table 13.a 80% Confidence Interval Based on the Observed ORR

[redacted]

N=18 patients.
ORR=overall response rate.

[redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. 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 federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

[redacted]

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

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

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

[redacted]

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

15.3 Patient Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

[redacted]

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 in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's 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 to find 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 callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, 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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

[redacted]

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Appendix A Schedule of Events

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Informed consent (b)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
HBV, HCV, and HIV	X								
Height and weight (c)	X	X				X			
ECOG performance status	X	X				X			
ECG (d)	X	X				X			
		ECG measurements additionally on **Days 2, 3**, and **4** for Cycles 1 and 2 (see Section 9.4.12).							
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).								
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).								
Dosing									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 injection (f)		X	X	X	X	X	X	X	X
Laboratory assessments									
Serum chemistry (g)	X	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X				X			

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Pregnancy test (j) (k)	X	X				X			
Response assessments for MM									
Investigator disease assessment (t)						X			
Serum M-protein	X	X				X			
Urine M-protein (l)	X	X				X			
Serum FLC assay (m)	X	X				X			
Immunofixation - serum and urine (n)	X	X				X			
Quantification of Ig	X	X				X			
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)	X								
Biological assessments									
Bone marrow aspiration (BMA) (p)	X					X			
Serum sample for TAK-079 PK (q)		X	X	X	X	X	X	X	X
		PK sampling additionally on **Days 2, 3**, and **4** for Cycles 1 and 2.							
[redacted]									
Serum sample for immunogenicity (ADA/titer) (s)		X		X		X			
Serum sample for direct and indirect Coombs test	X	X				X			

Footnotes appear on last page of SOE tables.

Treatment Period Continued: Cycles 3 Through 6

Study Period	Treatment Phase (Every 2 Weeks)
[redacted]	

(Phases 1 and 2a)	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Height and weight (c)	X		X		X		X	
ECOG performance status	X		X		X		X	
ECG (d)	X		X		X		X	
Physical examination	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).							
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).							
Dosing								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 injection (f)	X	X	X	X	X	X	X	X
Laboratory assessments								
Serum chemistry (g	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X
Urinalysis (i)	X		X		X		X	
Pregnancy test (j) (k)	X		X		X		X	
Response assessments for MM								
Investigator disease assessment (t)	X		X		X		X	
Serum M-protein	X		X		X		X	
Urine M-protein (l)	X		X		X		X	
Serum FLC assay (m)	X		X		X		X	
Immunofixation - serum and urine (n)	X		X		X		X	
Quantification of Ig	X		X		X		X	
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)							X	

[redacted]

Treatment Period Continued: Cycles 3 Through 6

Study Period (Phases 1 and 2a)	Treatment Phase (Every 2 Weeks)							
	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	C3D1	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15
Window Allowed	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days
Biological assessments								
Bone marrow aspiration (BMA) (p)			X					
Serum sample for TAK-079 PK (q)	X	X	X	X	X	X	X	X
[redacted]								
Serum sample for immunogenicity (ADA/titer) (s)	X		X		X		X	
Serum sample for direct and indirect Coombs test	X		X		X		X	

Footnotes appear on last page of SOE tables.

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	C7D1	C8D1, CXD1	Up to 30 days After Last Dose	--------	--------
Window Allowed	±2 days	±2 days	±7 days	± 7 days	± 7 days
Laboratory assessments					
Height and weight (c)	X	X	X		
ECOG performance status	X	X	X		

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	C7D1	C8D1, CXD1	Up to 30 days After Last Dose	--------	--------
Window Allowed	±2 days	±2 days	±7 days	± 7 days	± 7 days
ECG (d)	X	X	X		
Physical examination	X	X	X		
Vital signs (e)	X	X	X		
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3). **SAEs** (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).				
Dosing					
Pre-injection medication	X	X			
TAK-079 injection (f)	X	X			
Laboratory assessments					
Serum chemistry (g)	X	X	X		
Hematology (h)	X	X	X		
Urinalysis (i)	X	X	X		
Pregnancy test (j) (k)	X	X	X		
Response assessments for MM					
Investigator disease assessment (t)	X	X	X	X	
Serum M-protein	X	X	X	X	
Urine M-protein (l)	X	X	X	X	
Serum FLC assay (m)	X	X	X	X	
Immunofixation - serum and urine (n)	X	X	X		
Quantification of Ig	X	X	X		

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	**C7D1**	**C8D1, CXD1**	**Up to 30 days After Last Dose**	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Skeletal survey: WB X-ray, CT, low dose CT, PET-CT, or MRI scan (o)			X		
Biological assessments					
Bone marrow aspiration (BMA) (p)	X	X (Cycle 13 only)			
Serum sample for TAK-079 PK (q)	X	X	X		
[redacted]					
Serum sample for immunogenicity (ADA/titer) (s)	X	X	X		
Serum sample for direct and indirect Coombs test	X	X	X		
Subsequent anticancer therapy				X	X
Survival (u)					X

Footnotes begin on the next page.

[redacted]

ADA=antidrug antibody; AE=adverse event; BMA=bone marrow aspirate; [redacted]; C=cycle; CR=complete response; CT=computed tomography; CXD1=Day 1 of additional treatment cycles (ie, after Cycle 8); D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FLC=free light chain; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=Informed Consent Form; Ig=immunoglobulin; IMWG=International Myeloma Working Group; IR=injection reaction; MM=multiple myeloma; MRI=magnetic resonance imaging; OS=overall survival; PD=disease progression; PET-CT=positron emission tomography-computed tomography; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; RBC=red blood cell; SAE=serious adverse event; SOE=Schedule of Events; [redacted]; VGPR=very good partial response; WB=whole body; WBC=white blood cell.

(a) The screening period is 21 days (ie, Days -21 to Day -1).

(b) Written informed consent must be obtained before performing any protocol-specific procedure.

(c) Height will be measured only at the screening visit. Weight will be measured at indicated visits.

(d) A single ECG will be collected at the screening visit. PK time-matched triplicate 12-lead ECGs will be collected during Cycles 1 and 2, as specified in Appendix B. Single 12-lead ECGs will be administered for all other designated visits (ie, after Cycle 2).

(e) Vital signs are measured prior to TAK-079 injection. Blood pressure will also be measured before starting each 2 mL injection, and at any time the patient complains of symptoms consistent with IR. Vital signs include temperature, pulse, respiratory rate, and blood pressure.

(f) Time and anatomical site should be recorded for each injection (see Figure 6.a and Section 8.0).

(g) Serum β_2 microglobulin levels will be measured at screening only. Refer to Section 9.4.13.1 for a list of clinical chemistry laboratory assessments.

(h) Refer to Section 9.4.13.1 for a list of hematology laboratory assessments.

(i) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. Refer to Section 9.4.13.1 for a list of urinalysis assessments.

(j) Pregnancy test (Refer to Section 9.4.8): Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A serum pregnancy test will be performed during screening (within 10-14 days before start of study drug). A serum pregnancy test is required within 24 hours before start of study drug.

(k) Pregnancy test (refer to Section 9.4.8): On-treatment: a urine pregnancy test is required at designated study visits. A urine pregnancy test is required at the follow-up visit in women of childbearing potential. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.

(l) Sampling required only if urine M-protein is measurable at Day 1 (visit 2). Per IMWG, required in all patients for PR, VGPR, CR, at EOT, and to determine PD during PFS follow-up.

(m) Blood sample obtained for the serum FLC assay to include quantification of kappa and lambda chains and ratio). To be analyzed locally.

(n) Will also be collected to confirm a CR.

(o) May be performed up to 21 days before first dose of TAK-079. Additional surveys (x-ray, CT, or MRI) may be performed at the investigator's discretion, eg, in case of bone pain. If disease is documented, then a repeat scan should be performed as required to document a response or PD.

(p) BMAs: [redacted] At screening, a standard BMA drawn prior to consent is acceptable provided this is collected within 5 weeks before the first dose; cytogenetics will be done locally (See Section 9.4.14.6).
For response assessment purposes, when a CR is suspected based on laboratory values, a BMA is required to confirm a CR. At the time of this procedure (at CR), 1 aspirate sample is analyzed locally for evaluation of disease, [redacted]

(q) Blood samples for PK characterization will be collected at time points specified in Appendix B PK Sampling Schedule.
[redacted]

[redacted]

(s) Serum samples for immunogenicity assessment will be collected at baseline (before TAK-079 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.
(t) Patients who discontinue treatment for reasons other than PD will continue to be followed every 4 weeks until PD, death, start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first.
(u) Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

[redacted]

Appendix B PK Sampling Schedule

PK Assessments: Cycle 1

	Cycle 1										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

PK Assessments: Cycle 2

	Cycle 2										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG=electrocardiogram; PK=pharmacokinetic(s); SC=subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

PK Assessments: Cycle 3 to Cycle 10

	Cycle 3 to Cycle 6		**Cycle 7 to Cycle 10**
	Day 1 (a)	**Day 15 (a)**	**Day 1 (a)**
Predose (within 1 hour before first SC injection)	X	X	X

PK=pharmacokinetic; SC=subcutaneous.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.

[redacted]

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

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

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

[redacted]

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

[redacted]

Appendix E IMWG Criteria

IMWG Definition of MM [17,18,24]

- Clonal bone marrow plasma cells ≥10%* or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically.
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of the normal range or >2.75 mmol/L (>11 mg/dL).
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL).
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡.
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%.
  - Involved: uninvolved serum free light chain ratio§ (FLC) ≥100.
  - >1 focal lesions on MRI studies.

* Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
† Measured or estimated by validated equations.
‡ If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, United Kingdom). The involved FLC must be ≥100 mg/L. Each focal lesion must be 5 mm or greater in size [24].

[redacted]

IMWG Uniform Criteria for Response [17,18,24]

Category of Response	Response Criteria
sCR	Criteria for CR as defined below, with the addition of a normal FLC ratio, and an absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed (a).
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; 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; 2 consecutive assessments are needed (b).
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 >4 colors).
Molecular CR	CR as defined, plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; 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; 2 consecutive assessments are needed (c).
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed (a) no known evidence of progressive or new bone lesions if radiographic studies were performed.
Minimal response (MR) (b)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the 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 (c)	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

Source: Rajkumar SV et al, 2011 and Palumbo A et al, 2014 [17,18].
CR=complete response; FLC=free light chain; IMWG=International Myeloma Working Group; MR=minimal response; ORR=overall response rate; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.
(a) Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
(b) For relapse-refractory myeloma only.
(c) These categories do not contribute to the ORR.

Before the institution of any new therapy, sCR, CR, and VGPR 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.

PD is defined as an increase of ≥25% from lowest response value in any of the following:

a) Serum M-protein (absolute increase must be ≥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

b) Urine M-protein (absolute increase must be ≥200 mg/24 hour), and/or

c) Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL).

d) Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%).

OR

a) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

b) Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Clarifications to IMWG criteria for coding PD: 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 tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

[redacted]

Appendix F ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM et al, 1982 [19].
ECOG=Eastern Cooperative Oncology Group.

[redacted]

Appendix G Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: The study design was updated to reflect a maximum treatment duration of 12 months, unless a patient has clinical benefit that warrants continued treatment beyond 12 months.

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

Initial wording:	Patients will receive TAK-079 until they experience PD as defined by IMWG for patients with MM ([9,10]; Appendix E), unacceptable toxicity, withdrawal of consent, death, termination of the study by the sponsor, until any other discontinuation criterion is met, or until 12 months after LPLD (additional participation details are provided in Sections 6.1, 8.4.3, 9.6, and 9.7).
Amended or new wording:	Patients will receive TAK-079 until they experience PD as defined by IMWG ~~for patients with MM (~~**criteria [17,18]** (Appendix E), unacceptable toxicity, ~~withdrawal of consent, death, termination of the study by the sponsor, until~~ **or** any other discontinuation criterion is met~~, or until 12 months after LPLD (additional participation details are provided in Sections 6.1, 8.4.3, 9.6,~~ **(see Section 8.4.3 and Section 9.7**).**The maximum duration of treatment is expected to be 12 months; however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment beyond 1 year with the explicit approval of the sponsor's study clinician.**

Rationale for Change:

This change was made to clarify the duration of treatment for all patients and to require evidence of disease response to stay on therapy for more than 12 months.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting.
- Section 6.3.4 Total Study Duration.

Change 2: Maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) was clarified to be a secondary objective/endpoint.

The primary change occurs in Section 5.2.3 Phase 1 Secondary Endpoints:

Added text: The secondary endpoints for phase 1 are:

- **RP2D based on both safety and efficacy outcomes**

[redacted]

Rationale for Change:

This change was made to correct an inconsistency in the protocol.

Section 2.0 STUDY SUMMARY also contains this change.

Change 3: Time-to-event measures were added as a secondary objective.

The primary change occurs in Section 5.1.2 Secondary Objectives:

Added text: The **Phase 2a** secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- **To provide a preliminary evaluation of time-to-event measures.**
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

Rationale for Change:

This change was made to correct an inconsistency in the protocol.

Section 2.0 STUDY SUMMARY also contains this change.

Change 4: [redacted].

The primary change occurs in Section 5.1.3 Exploratory Objectives:

Initial wording: [redacted]

Amended or new wording: [redacted]

[redacted]

Rationale for Change:

These changes were made to clarify the [redacted] to better align with the mechanism of action of TAK-079 and to reduce sample collection burden on patients.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 5.2.5 Exploratory Endpoints.
- Table 9.c Primary Specimen Collection.
- Section 9.4.15.1 Primary Specimen Collection for PK, [redacted], and [redacted]
- Section 9.4.15.3 [redacted]
- Appendix A Schedule of Events.

Change 5: Dosing procedures after Cycle 1 Day 1 in the setting of no systemic infusion reactions (IRs) were clarified.

The primary change occurs in Section 8.1.2 TAK-079 Formulation and Administration:

Initial wording:	After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL), injected every 30 minutes until the full scheduled dose has been administered. Patients may receive low-dose methylprednisolone (≤ 20 mg) for the prevention of delayed injection related reaction, as clinically indicated.
Amended or new	After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL~~), injected every 30 minutes until the full scheduled dose~~ [redacted]

wording: ~~has been administered~~**). For dose levels where multiple SC injections are needed to administer the full prescribed dose (ie, 300 mg dose and above), the Cycle 1 Day 1 dose will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all drug administration days after Cycle 1 Day 1, if the patient did not have a clinically significant IR per the investigator, the SC injections can be given at the at the same time without a waiting period.**

~~Patients may receive low-dose methylprednisolone (≤ 20 mg) for the prevention of delayed injection related reaction, as clinically indicated.~~

When patients are to receive multiple SC injections, 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.

Rationale for Change:

This change was made to clarify procedures in the protocol to simplify dosing for patients who do not experience an IR on Cycle 1 Day 1.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Figure 6.a Overall Study Schematic Diagram.

Change 6: Predose and postdose medications were clarified.

The primary change occurs in Section 8.1.1 Predose and Postdose Medication (formerly titled Premedications):

Initial wording:

8.1.1 Premedication

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor) is optional for Cycle 1 Day 1.

NOTE: Patients with a higher risk of respiratory complications (eg, patients with a history of COPD and patients with asthma) will be treated with postinjection medication consisting of the following:

[redacted]

- An antihistamine (diphenhydramine or equivalent) on the first and second days after all injections,
- A short-acting β_2 adrenergic receptor agonist, such as salbutamol (albuterol) aerosol, and
- Control medications for lung disease (eg, inhaled corticosteroids with or without long-acting β_2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol with or without inhaled corticosteroids for patients with COPD).

Premedication will be mandatory in phase 1. The decision to premedicate in phase 2a will be determined based on data from phase 1.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

Amended or new wording:

8.1.1 ~~Premedication~~Predose and Postdose Medication

Predose Medication

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor) ~~is optional for Cycle 1 Day 1~~.

NOTE: ~~Patients with a higher risk of respiratory complications (eg,~~**For any** patients with a history of ~~COPD and patients with asthma) will be treated with postinjection medication consisting of the following:~~

- ~~An antihistamine (diphenhydramine or equivalent) on the first and second days after all injections,~~
- ~~A short-acting β_2 adrenergic receptor agonist, such as salbutamol (albuterol) aerosol, and~~

~~Control~~ **COPD, consider prescribing postinfusion** medications ~~for lung disease (eg, inhaled corticosteroids with or without long-acting β_2 adrenergic receptor agonists for patients with asthma;~~ **such as short- and** long-acting bronchodilators ~~such as tiotropium or salmeterol with or without~~**, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional** inhaled ~~corticosteroids for patients with COPD).~~**postinfusion medications may be**

[redacted]

discontinued.

Premedication~~s will be mandatory~~ **are required** in phase 1~~. The decision to premedicate in~~ **and** phase 2a ~~will be determined based on data from phase 1~~.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

Postdose Medications

Postinjection site care: **Apply 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).**

Patients may receive low-dose methylprednisolone (<20 mg) for the prevention of delayed injection-related reaction as clinically indicated after an injection.

Rationale for Change:

This change was made to clarify procedures in the protocol. Required premedications were updated for consistency across the 2 phases of the study. Postdose prophylactic care was added to minimize any potential injection site reactions.

Section 2.0 STUDY SUMMARY also contains this change.

Change 7: The periods of patient evaluation at end of treatment (EOT) and for progression-free survival (PFS) and overall survival (OS) were clarified throughout, including the estimated duration of the study and end-of-study reporting.

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

Initial wording:

- Follow-up Period (follow-up visit): Patients who discontinue for PD will be followed for 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks until PD, death, loss to follow-up, consent withdrawal, study termination, or 12 months after the last patient has received their last dose (last patient, last dose [LPLD]). All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, study termination, or 12 months after LPLD.

…

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined. The estimated duration of the study is approximately 48 months (4 years; Section 6.3).

Amended or new

- Follow-up ~~P~~**p**eriod (~~follow-up~~**EOT** visit): Patients who discontinue ~~for PD~~**study treatment** will be followed for **approximately** 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor

[redacted]

wording: safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks **from the EOT visit** until PD, death, ~~loss to follow-up, consent withdrawal~~**the start of subsequent anticancer therapy**, study termination, or 12 months after ~~the last patient has received their last dose (last patient, last dose [LPLD]).~~**discontinuation of study treatment, whichever occurs first. Patients who discontinue for PD will be followed for OS after the EOT visit.** All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, **or** study termination~~, or 12 months after LPLD~~.

…

It is expected that approximately 42 patients will be enrolled in total for phase 1 and 2a combined. ~~The estimated duration of the study is approximately 48 months (4 years; Section 6.3)~~.

Rationale for Change:

This change was made to correct inconsistencies in the protocol.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.3.1 Duration of an Individual Patient's Study Participation.
- Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting.
- Section 6.3.4 Total Study Duration
- Section 9.4.3 Medical History.
- Section 9.6 Completion of Study (for Individual Patients).
- Section 9.10 Posttreatment Follow-up Assessments (PFS and OS).
- Appendix A Schedule of Events.

[redacted]

Change 8: The time since last prior antineoplastic therapy was clarified.

The primary change occurs in Table 7.a Required Washout Periods for Previous Treatments or Procedures Prior to Administration of TAK-079:

Initial wording:

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	30 days
Antibody therapy (including anti-CD38)	120 days
Corticosteroid therapy (a)	30 days
Autologous transplantation	90 days
Radiation therapy	30 days
Major surgery	30 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.

Amended or new wording:

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	~~30~~14 days
Antibody therapy (including anti-CD38)	~~120~~180 days
Corticosteroid therapy (a)	~~30~~7 days
Autologous transplantation	90 days
Radiation therapy **(b)**	~~30~~14 days
Major surgery	~~30~~14 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.
(b) Prophylactic "spot" radiation for areas of pain is permitted.

Rationale for Change:

These changes were made to align with good clinical practice for patients with RRMM and permit patients to have fast access to subsequent therapy while ensuring an adequate wash out period from prior treatment.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 7.2 Exclusion Criteria.

Change 9: [redacted]

The primary change occurs in Section 9.4.13 Clinical Laboratory Evaluations:

Initial wording: CD38 expression will be assessed by multicolor flow cytometry, and patients who express CD38 with a mean fluorescence intensity ≥1000 units on ≥90% of plasma cells will be eligible for inclusion into the trial. [redacted]

[redacted]

	[redacted] CD38 expression will be assessed locally for both phase 1 and phase 2a for enrollment into the study then confirmed centrally.
Amended or new wording:	CD38 expression **of MM cells** will be assessed by multicolor flow cytometry~~, and patients who express CD38 with a mean fluorescence intensity ≥1000 units on ≥90% of plasma cells will be eligible for inclusion into the trial.~~**; analysis will be done centrally.** [redacted] ~~CD38 expression will be assessed locally for both phase 1 and phase 2a for enrollment into the study then confirmed centrally.~~

Rationale for Change:

This change was made because now CD38 testing will be performed on study by the central laboratory to ensure consistency across patients.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 7.1 Inclusion Criteria.
- Section 9.4.13 Clinical Laboratory Evaluations
- Section 9.4.15.3 [redacted].

Change 10: Active cytomegalovirus infection was removed from the list of excluded infections.

The primary change occurs in Section 7.2 Exclusion Criteria:

Initial wording:	15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, active HIV, or cytomegalovirus (CMV) infection.
Amended or new wording:	15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, **or** active HIV~~, or cytomegalovirus (CMV)~~ infection.

Rationale for Change:

This change was made to correct the exclusion criteria.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 9.4.3 Medical History.
- Appendix A Schedule of Events.

[redacted]

Change 11: Assessments of clinically significant laboratory values and vital signs were removed from the phase 1 primary endpoints as these are included in the definition of treatment-emergent adverse events (TEAEs).

The primary change occurs in Section 5.2.1 Phase 1 Primary Endpoints:

Deleted text:

- The number of patients with TEAEs overall and per dose level.
  - Patients with dose-limiting toxicities (DLTs) at each dose level.
  - Patients with Grade ≥3 TEAEs.
  - Patients with SAEs.
  - Patients who discontinue because of TEAEs.
  - Patients with dose modifications (delays, interruptions, dose reductions).
  - ~~Clinically significant laboratory values, as determined by the investigator.~~
  - ~~Clinically significant vital sign measurements, as determined by the investigator.~~

Rationale for Change:

Clinically significant laboratory values and vital signs will be captured as part of TEAE evaluation. As a result, this change was made to simplify the study objectives.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 5.2.4 Phase 2a Secondary Endpoints
- Table 6.a Primary and Secondary Endpoints for Disclosures.

[redacted]

Change 12: Details on nonclinical studies with TAK-079 were added.

The primary change occurs in Section 4.2 Findings From Nonclinical and Clinical Studies:

Added text: [redacted] **Human erythrocytes [7] and platelets [8] express low levels of CD38, and the presence of erythrophagocytosis in the marrow suggests an immune-mediated component. The absence of erythrophagocytosis in the spleen, lymph nodes, and liver suggests that immune-mediated anemia did not result from targeting of mature erythrocytes. In an investigative study, binding of TAK-079 to cynomolgus or human RBCs or platelets from 30 different donors was not detected; however, a more sensitive assay did subsequently detect binding of TAK-079 to CD38+ expressed on human erythrocytes, which is consistent with binding of daratumumab to human RBCs. A mid-to-low level of CD38+ expression is reportedly present on erythrocytes and megakaryocyte erythroid progenitors. This was confirmed as moderate-to-marked membranous TAK-079 positive staining of hematopoietic cells in human bone marrow, which suggests targeting of progenitor cells as the mechanism of anemia and thrombocytopenia.**

Rationale for Change:

The text was added to support the study rationale.

The following sections also contain this change:

- Section 4.3.1.1 Infusion and Injection Site Reactions.
- Section 4.3.1.3 Hematologic Effects.

Change 13: Details about management of IRs and injection site reactions were added.

The primary change occurs in Section 8.8 Management of Specific Adverse Reactions:

Initial wording:

8.8.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of Grade 1 or 2 infusion reactions:

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.

In case of Grade 3 infusion reactions:

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached and therefore skip remaining dose) until next scheduled TAK-079 SC administration, providing that infusion reactions have recovered to Grade ≤1 at the moment of the next scheduled TAK-079 dose.
- Permanently discontinue treatment after the 3rd occurrence of Grade 3 infusion reactions

In case of Grade 4 infusion reactions:

- Permanently discontinue treatment.

In case of an IR, blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

For additional details, refer to Section 9.4.15.3

Amended or new wording:

8.8.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any **systemic** IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

~~In case of Grade 1 or 2 infusion reactions:~~ In case of an IR (any grade), blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

[redacted]

For additional details, refer to Section 9.4.15.3.

Grade 1 or 2 IR

In case of Grade 1 or 2 IRs (systemic signs or symptoms):

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.
    - **If a patient experiences a Grade 1 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once the patient is stable per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.**
    - **If a patient experiences a Grade 2 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once resolved to Grade 1 or resolved completely, per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.**
  - **Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. Subsequent doses may have individual SC injections administered more frequently at the investigator's discretion with appropriate premedication and postmedication.**

Grade 3 IR

In case of Grade 3 ~~infusion reactions:~~ **IRs (systemic signs or symptoms):**

- Withhold therapy (also administration of remaining SC injections ~~when~~**if** full dose was not yet reached and therefore skip remaining ~~dose~~**injection[s]**) until next scheduled TAK-079 SC administration, providing that ~~infusion reactions have~~ **the IR has** recovered to Grade ≤1 at the ~~moment~~**time** of the next scheduled TAK-079 dose. **Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. At the time of the next dose after an IR, patients at a dose level requiring more than 1 SC injection should receive each injection 30 minutes apart. If no further IR, subsequent injections may be given more frequently at the investigator's discretion with appropriate premedication and postmedication.**
- Permanently discontinue treatment after the ~~3rd~~**third** occurrence of Grade 3 ~~infusion reactions~~**IRs.**

[redacted]

Grade 4 IRs

In case of Grade 4 ~~infusion reactions~~ **IRs (systemic signs or symptoms)**:

- Permanently discontinue treatment.

8.8.2 ~~In case of an IR~~Injection Site Care

Prophylactic post-injection site care:

- **Apply 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).

Rationale for Change:

This change was made to clarify procedures in the protocol and to assist investigators in the management of IRs/injection site reactions that may occur.

Section 4.3.1.1 Infusion and Injection Site Reactions also contains this change.

[redacted]

Change 14: The procedures for monitoring all infections were clarified.

The primary change occurs in Section 4.3.1.4 Infections:

Initial wording:	*4.3.1.5 Serious Infections* In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections. Subjects will be monitored for any signs and symptoms of the important potential risk of serious infections throughout this clinical study (see Section 8.8.4).
Amended or new wording:	~~*4.3.1.5*~~ ***4.3.1.4*** ~~*Serious*~~ *Infections* In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections. Subjects will be monitored for any signs and symptoms of ~~the important potential risk of serious~~ infections throughout this clinical study (see Section 8.8.4).

Rationale for Change:

This change was made to clarify that all infections will be assessed in the study, not just serious infections.

The following sections also contain this change:

- Section 4.3.1 Potential Risks.
- Section 4.3.2 Overall Benefit and Risk Assessment for This Study.

[redacted]

Change 15: The rationale for the proposed study was revised, including presentation of results from the healthy subject study.

The primary change occurs in Section 4.4 Rationale for the Proposed Study:

Initial wording:	TAK-079 binds a partially distinct epitope of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab. Unlike daratumumab, TAK-079 does not bind to RBCs and platelets. Therefore, TAK-079 may possess higher tumoricidal activity than daratumumab because cytolytic effector activity is focused on CD38+ leukocytes/tumors and is not misdirected to RBCs and platelets. Consequently, TAK-079 may demonstrate higher potency (ie, activity at lower doses and exposures) and activity in daratumumab-refractory tumors (ie, tumors expressing lower levels of CD38) and thus be more efficient at eliminating tumors. In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed. In summary, it is feasible to investigate administration of TAK-079 in patients with relapsed or refractory (r/r) MM.
Amended or new wording:	TAK-079 binds ~~a partially distinct epitope~~**to unique amino acids** of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab. ~~Unlike daratumumab, TAK-079 does not bind to RBCs and platelets. Therefore, TAK-079 may possess higher tumoricidal activity than daratumumab because cytolytic effector activity is focused on CD38+ leukocytes/tumors and is not misdirected to RBCs and platelets. Consequently, TAK-079 may demonstrate higher potency (ie, activity at lower doses and exposures) and activity in daratumumab-refractory tumors (ie, tumors expressing lower levels of CD38) and thus be more efficient at eliminating tumors.~~ In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed. **For example, NK cells were reduced >90% from baseline levels in all healthy subjects receiving a single 0.06 mg/kg IV dose of TAK-079 and exhibited a mean C_{max} of 0.1 ug/mL (TAK-079_101). Comparable depletion of NK cells by daratumumab administered IV to a population of patients with refractory MM [12] required doses of >24 mg/kg and a mean C_{max} of >500 ug/mL [13,14]. Consequently, TAK-079 may be significantly more efficient at eliminating target cells in patients, which could manifest as higher activity on tumor cells (ie, activity at lower doses, low-volume SC administration, and less frequent administration), including activity on daratumumab-refractory tumors. The potential activity of TAK-079 should therefore be investigated in patients with** relapsed and/or

refractory multiple myeloma (**RRMM).**

~~In summary, it is feasible to investigate administration of TAK-079 in patients with relapsed or refractory (r/r) MM.~~

Rationale for Change:

This change was made to provide additional details for the study rationale on the basis of newly learned data.

The following sections also contain this change:

- Section 4.4.1 Rationale for the Starting Dose of TAK-079.
- Section 4.3.1.1 Infusion and Injection Site Reactions.

Change 16: The time required for highly effective contraception in women of childbearing potential (WOCBP) and in male patients was clarified for consistency.

The primary change occurs in Section 8.7 Precautions and Restrictions:

Initial wording:

Female patients must meet the following:

…

- 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 5 half-lives after the last dose of study drug (whichever is longer), OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and 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 one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR

Amended or new wording:

Female patients must meet the following:

…

- 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 **at least 90 days or** 5 half-lives after the last dose of study drug (whichever is longer), OR

[redacted]

…

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

- Agree to practice effective barrier contraception during the entire study treatment period and through ~~120~~**90** days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR

Rationale for Change:

This change was made to correct an inconsistency between the protocol and IB.

Section 7.1 Inclusion Criteria also contains this change.

Change 17: The exclusion criterion about recovery from prior myeloma treatments was clarified to exclude alopecia.

The primary change occurs in Section 7.2 Exclusion Criteria:

Added text: 4. Not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE Grade ≤1 or baseline**, excluding alopecia**.

Rationale for Change:

This change was made to clarify that alopecia is not a clinically significant toxicity that patients need to recover from before entering the study,

Change 18: DLT assessments and withdrawal/replacement of patients were clarified.

The primary change occurs in Section 8.2 Definitions of DLT:

Added text: **Patients who experience a DLT should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort; such patients will not count as a patient in that lower dose cohort for escalation decisions.**

In phase 1, patients who do not receive 4 full doses of TAK-079 within the 28-day (±2) treatment window or the Day 29 (ie, Cycle 2 Day 1) assessment for reasons other than a DLT will be replaced. Patients experiencing a DLT should not be replaced.

Rationale for Change:

These changes were made to clarify the study procedures.

The following sections also contain this change:

- Section 8.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle.

[redacted]

- Section 8.4.2 Criteria for Dose Modification.
- Section 8.4.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification).
- Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement.

Change 19: A sentence summarizing the definition of the MTD has been added.

The primary change occurs in Section 8.3.2 Escalation Schema:

Initial wording:	If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3 patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and the lower dose level may be considered the MTD.
Amended or new wording:	• If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3 patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and ~~the lower~~**this** dose level may be considered the MTD**. The MTD is defined as the highest dose with a cohort of 6 patients having no more than 1 patient with a DLT**.

Rationale for Change:

The change was made to clarify the study procedures.

Change 20: The criteria for beginning or delaying a subsequent treatment cycle were clarified.

The primary change occurs in Section 8.4.2 Criteria for Dose Modification:

Initial wording:	**8.4.2 Criteria for Dose Reduction** All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held, may have their dose reduced, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, 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 study drug may be treated as per local standard of care, dose-modifications, interruptions and permanent discontinuations may be discussed upfront with the medical monitor. Table 8.a provides general dose modification recommendations. When the dose of

TAK-079 is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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. See details for managing specific AEs in Section 8.8.

[Table 8.a Dose Modification Recommendations for TAK-079 Toxicities]

When a dose reduction occurs, the TAK-079 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-079 can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-079 because of AE are generally recommended.

If dose-reduction is not possible because the lowest dose-level has already been reached, treatment may be permanently discontinued.

The dose of TAK-079 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

Amended or new wording:

8.4.2 Criteria for Dose ~~Reduction~~Modification

All toxicities that occur during the study will be actively managed following ~~the~~**medical** standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held~~, may have their dose reduced~~, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, 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 study drug 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 TAK-079.**

Table 8.a provides general dose modification recommendations. When the dose of TAK-079 is withheld on the basis of these criteria, clinical and laboratory

re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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 monoclonal antibodies as a means to reduce dose intensity [5,21,22]. Patients experiencing a DLT (defined in Section 8.2) should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort.**

See details for managing specific AEs in Section 8.8.

[Table 8.a Dose Modification Recommendations for TAK-079 Toxicities: ***removed all mention of dose reductions; clarification added for assessment of DLTs and other AEs*****]**

~~When a dose reduction occurs, the TAK-079 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-079 can be further reduced if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced, it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-079 because of AE are generally recommended.~~

~~If dose reduction is not possible because the lowest dose level has already been reached, treatment may be permanently discontinued.~~

~~The dose of TAK-079 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.~~**If initial dose interruption does not provide sufficient relief, the dose of TAK-079 should be considered for permanent discontinuation.**

[New Table 8.b TAK-079 Related Toxicity Management]

A TAK-079 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. Subjects missing ≥3 consecutive planned doses of TAK-079 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 TAK-079 during every-4-weeks dosing may be delayed (interrupted) up to 4 weeks. 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 TAK-079 that requires a dose delay (interruption) of more than 28 days should result in permanent discontinuation of TAK-079, unless both the investigator and the sponsor study clinician believe the patient is deriving clinical benefit.

Rationale for Change:

The change was made to clarify that toxicity is managed by means of dose interruptions, including missed doses, as is standard with administration of monoclonal antibodies as a means to reduce dose intensity.

Section that also contain this change are:

- Section 8.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle.
- Section 8.4.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification).

Change 21: Disease response assessments, including imaging and laboratory testing, were clarified.

The primary change occurs in Section 9.4.14 Disease Response Assessments:

Initial wording:	Patients will be assessed for disease response according to the IMWG for MM ([9,10]; Appendix E). Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079. Imaging tests as specified in Appendix A are to be performed as defined below or when there is a need to document a response or a disease progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase prior to treatment and every 6 cycles thereafter until PD or intolerance. Additional surveys (x-ray, CT, or MRI) will be performed at the investigator's discretion (eg, in case of bone pain) to document a response or progressive disease. The same imaging technique should be used throughout the study to facilitate consistent disease assessment. CR should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.
Amended or new wording:	Patients will be assessed for disease response according to the IMWG ~~for MM~~**criteria** (~~9,10~~**[17,18]**; Appendix E). Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079. **Patients measurable by SPEP only will have 24-hour urine collected at screening and**

[redacted]

EOT and to document PR, VGPR, CR, or PD.

~~Imaging tests as specified in Appendix A are to be performed as defined below or when there is a need to document a response or a disease progression. Response and relapse categories are described in Appendix E. Imaging tests will be taken during the screening phase prior to treatment and every 6 cycles thereafter until PD or intolerance. Additional surveys (x-ray, CT, or MRI) will be performed at the investigator's discretion (eg, in case of bone pain) to document a response or progressive disease.~~**Imaging tests will be done per Appendix A and as described in Section 9.4.14.1**. The same imaging technique should be used throughout the study to facilitate consistent disease assessment.

~~CR~~ **Responses** should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.

…

Blood samples, 24-hour urine sample, BMA, and imaging done for disease response assessment will be done locally.

Rationale for Change:

The change was made to clarify the study procedures to better align with IMWG criteria.

The following sections also contain this change:

- Section 9.4.14.1 Computed Tomography/Magnetic Resonance Imaging.
- Section 9.4.14.2 Quantification of Immunoglobulins.
- Section 9.4.14.3 Quantification of M-Protein.
- Section 9.4.14.4 Serum FLC Assay.
- Section 9.4.14.5 Immunofixation of Serum and Urine.
- Section 9.4.14.6 BMAs.

Change 22: "Other" was added as a reason for treatment discontinuation or withdrawal of subject from study.

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

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

- AE/SAE.
- Protocol deviation.

[redacted]

- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.
- **Other.**

Rationale for Change:

The change was made to account for reasons not otherwise categorized.

Section 9.8 Withdrawal of Patients From Study also contains this change.

Change 23: The time required to monitor ongoing adverse events (AEs) after the end of study treatment was clarified.

The primary change occurs in Section 10.3 Monitoring of AEs and Period of Observation:

Added text: 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 next-line subsequent anticancer therapy, or 6 months after PD has occurred, whichever comes first.**

Rationale for Change:

The change was made to clarify the study procedures to allow for a longer window to monitor AEs after completion of treatment.

Change 24: Investigator disease assessments were added to the Schedule of Events (SOE).

The primary change occurs in Appendix A Schedule of Events:

Description of change: Added a row for "Investigator disease response" with assessments on Day 1 of every cycle starting at Cycle 2, at the EOT visit, and during PFS follow-up.

Rationale for Change:

The change was made to correct an error in the study procedures.

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	22-May-2018 18:39 UTC
[redacted]	Clinical Science Approval	22-May-2018 19:40 UTC
[redacted]	Clinical Science Approval	23-May-2018 07:23 UTC

PROTOCOL

A Phase 1/2a Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000

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

Study Number: TAK-079-1501

IND Number: 136,414 **EudraCT Number:** Not applicable

Compound: TAK-079

Date: 02 April 2019 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Region
12 October 2017	Initial Protocol	Global
08 December 2017	01	Global
18 May 2018	02	Global
02 April 2019	03	Global

[redacted]

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.0 and relevant guidelines provided to the site.

Contact Type/Role	United States Contact
SAE and pregnancy reporting	See Section 10.0

[redacted]

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 on Harmonisation E6 Good Clinical Practice: 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, PhD
Global Medical Affairs
Distinguished Research Fellow Oncology
Date

[redacted], PhD
Global Statistics
Date

[redacted], RN, MSN
Oncology Clinical Research
Date

[redacted]

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D 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)

[redacted]

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment 03. The primary reason for this amendment is to allow for an increase in the number of patients enrolled to the phase 1 period to further evaluate the safety, pharmacokinetics (PK), [redacted], to further inform the recommended phase 2 dose (RP2D) on the basis of available data from the dose Escalation Cohorts. Additionally, a cohort of patients is being added to evaluate TAK-079 combined with the backbone regimen of pomalidomide and dexamethasone (PomDex) in patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least 2 prior therapies and are refractory to the last therapy before study entry. Data is emerging that treatment options are needed for patients who have been exposed or are refractory to lenalidomide because of its increase use as initial therapy. PomDex is approved for this patient population and adding an anti-CD38 monoclonal antibody to it, especially one that is given subcutaneously (SC), could be beneficial and convenient for patients. As a result of adding the cohort of TAK-079 added to PomDex, relevant details and references about the administration of pomalidomide, including the Pomalyst Risk Evaluation and Mitigation Strategy (REMS), have been added.

Other minor changes were made throughout the protocol for clarification and to ensure consistency with the major changes described above.

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

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

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** TAK-079	
Title of Protocol: A Phase 1/2a, Open-label, Dose-Escalation Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of TAK-079 Administered Subcutaneously as a Single Agent in Patients With Relapsed/Refractory Multiple Myeloma		
Study Number: TAK-079-1501	**Phase:** 1/2a	

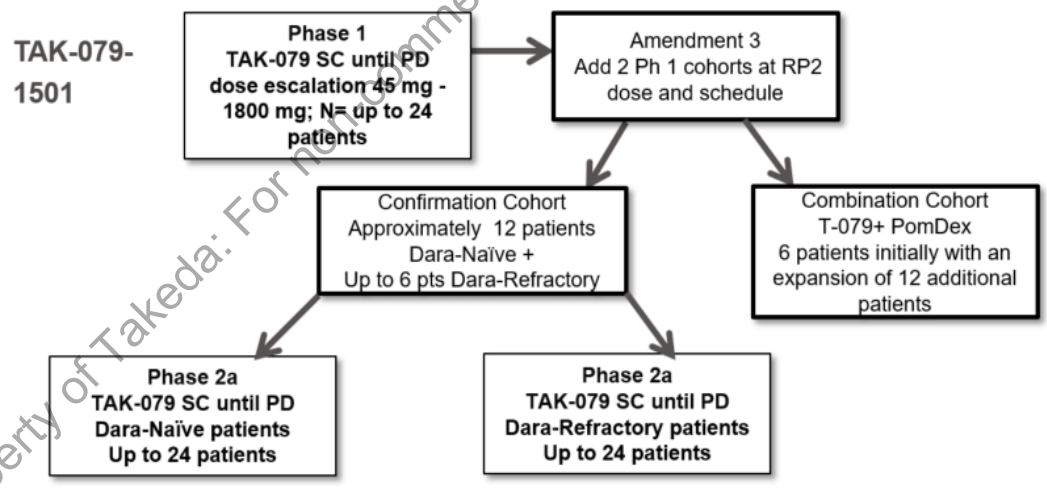
Study Design:

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients relapsed and/or refractory multiple myeloma (RRMM), and to provide a preliminary assessment of its activity against multiple myeloma (MM).

Once enrolled into the study, patients will receive TAK-079 via subcutaneous (SC) administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until disease progression (PD). Patients will receive ongoing treatment with TAK-079 until PD, unacceptable toxicities, or withdrawal due to other reasons.

The phase 1 portion of the study will evaluate administration of single agent TAK-079 for dose-limiting toxicity (DLT) to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) for further assessment in phase 2a. A recommended dose below the MTD may be identified based on the review of safety, pharmacokinetic (PK), [redacted], and clinical data from the phase 1 portion of the study.

Study Schema Figure:



Dara: daratumumab; PomDex: pomalidomide and dexamethasone; PD: progressive disease; disease progression; RP2: recommended phase 2; SC: subcutaneous.

The safety and tolerability of TAK-079 will be assessed by recording and analyzing treatment-emergent adverse events (TEAEs), dose modifications, treatment discontinuations, vital signs, physical examinations, serum chemistry and hematology, urinalysis, electrocardiograms (ECGs), and concomitant medications. In phase 1, approximately 6

doses of TAK-079 will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D (as per Study Schema Figure) before enrolling in the Phase 2a portion of the study. In the phase 2a portion of this study, Grade 4 or higher nonhematologic toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients thereafter. Additionally, a cohort of patients will evaluate TAK-079 combined with the backbone regimen of pomalidomide and dexamethasone (PomDex) in patients with RRMM who have received at least 2 prior therapies and are refractory to the last therapy before study entry (as per Study Schema Figure).

It is expected that approximately 100 patients will be enrolled in the study. The maximum duration of treatment is expected to be 12 months for patients receiving monotherapy and approximately 18 months for patients in the combination cohort; however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment with the explicit approval of the sponsor's study clinician. The estimated duration of the study is approximately 42 months (ie, 3.5 years).

Primary Objectives:

Phase 1

To determine the safety and tolerability of TAK-079 monotherapy and when combined with a backbone regimen of PomDex in patients with RRMM.

Phase 2a

To provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with RRMM.

Secondary Objectives:

Phase 1

The phase 1 secondary objectives are:

- To investigate a potential MTD/RP2D of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To evaluate the immunogenicity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To characterize the PK of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To provide a preliminary evaluation of the clinical activity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.

Phase 2a

The phase 2a secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To provide a preliminary evaluation of time-to-event measures.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

Exploratory Objectives:

Phase 1 and 2a

[redacted]

[redacted]

[redacted]

Subject Population: Subjects aged 18 years or older, with RRMM and Eastern Cooperative Group (ECOG) performance status of ≤2

Number of Subjects:	**Number of Sites:**
Phase 1: approximately 55 patients. Phase 2a: approximately 48 patients.	approximately 7 investigational centers.
Dose Level(s):	**Route of Administration:**
TAK-079 injections will be escalated as follows: 45 mg, 135 mg, 300 mg, 600 mg, 1200 mg, and 1800 mg in phase 1. After patients have received premedication treatment, doses will be administered with syringes as SC injections up to a maximum of 200 mg TAK-079 in 2 mL per injection. For dose levels where multiple SC injections are needed to administer the full prescribed dose (ie, 300 mg dose and above), the Cycle 1 Day 1 dose will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all drug administration days after Cycle 1 Day 1, if the patient did not have an infusion reaction (IR), the SC injections can be given at the same time without a waiting period. For phase 1 (Escalation Cohorts, dose Confirmation and Combination Cohorts) each dose or TAK-079 will be administered as once weekly for 8 weeks (8 doses), then once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks until PD or unacceptable toxicities occur. In the phase 1 combination cohort only, PomDex will be administered per package instructions. For phase 2a, in the absence of DLT, the dose will be selected based upon review of the available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study. Premedication will be mandatory in phase 1 and phase 2a.	Route of administration will be SC.

[redacted]

Duration of Treatment:	**Period of Evaluation:**
TAK-079 will be administered until the patient experiences PD, unacceptable toxicities, or withdrawal due to other reasons. The maximum duration of treatment is expected to be 12 months for patients receiving monotherapy and approximately 18 months for patients in the combination cohort; however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment with the explicit approval of the sponsor's study clinician.	21 days screening, ongoing treatment to PD. Patients who discontinue treatment for reasons other than PD will continue to be followed for progression-free survival (PFS) every 4 weeks from the end-of-treatment visit until PD, death, the start of subsequent anticancer therapy, study termination, or until 12 months after discontinuation of study treatment, whichever occurs first. Overall survival (OS): Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

Main Criteria for Inclusion:

Male and female patients, aged ≥18 years, with ECOG performance status of ≤2, requiring additional therapy as determined by the investigator. Patients must have received the final dose of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079: 180 days for antibody therapy (including anti-CD38); 90 days for autologous transplantation; 14 days for chemotherapy, radiation therapy, and major surgery; and 7 days for corticosteroid therapy (up to systemic equivalent of 10 mg daily prednisone allowed). Patients must have adequate organ function as determined by the following laboratory values: absolute neutrophil count $\geq 1.0\times10^9$/L; platelets ≥75,000/mm^3 ($\geq 75\times10^9$/L); hemoglobin ≥7.5 g/dL; creatinine clearance ≥30 mL/min (Cockcroft-Gault formula); total bilirubin ≤1.5 times the upper limit of the normal range (ULN); and alanine aminotransferase/aspartate aminotransferase ≤2.5×ULN. Patients must have documented RRMM per the International Myeloma Working Group (IMWG) criteria, with measurable disease defined as one of the following: serum M-protein ≥ 0.5 g/dL (≥5 g/L) and urine M-protein ≥200 mg/24 hours. Patients without measurable M-protein in serum protein electrophoresis or urine protein electrophoresis must have a serum free light chain (FLC) assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal. Patients must have evidence of RRMM as defined by the IMWG criteria. For patients in the Escalation Cohort and dose Confirmation Cohort: previously received myeloma therapy including a proteasome inhibitor (PI), immunomodulatory drug (IMiD), and steroids; refractory or intolerant to at least 1 PI and at least 1 IMiD; either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMiD; in phase 1, previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required for patients in the dose Escalation Cohort. Patients in the Combination Cohort (TAK-079 added to PomDex cohort only): have undergone prior therapy with ≥2 prior anti-myeloma therapies; has either relapsed or relapsed and refractory disease; have progressed on or within 60 days of completing the last anti-myeloma therapy; patients may be either naïve or exposed to prior anti-CD38 monoclonal antibodies; however there will be a cohort of patients refractory to at least 1 anti-CD38 mAb therapy at any time during treatment and one that is naïve to a prior anti-CD38 mAb. In the phase 2a portion of the study, up to 2 cohorts of patients with RRMM may be enrolled: one that is refractory to at least 1 anti-CD38 mAb therapy at any time during treatment and one that is naïve to prior anti-CD38 mAb.

Main Criteria for Exclusion:

Sensory or motor neuropathy of Grade ≥3, based on the National Cancer Institute Common Criteria for Adverse Events (NCI CTCAE) or not recovered from adverse reactions to prior myeloma treatments/procedures to NCI CTCAE Grade ≤1 or baseline; allogeneic stem cell transplant; congestive heart failure (New York Heart Association) Grade ≥II, cardiac myopathy, active ischemia, clinically significant arrhythmia, history of acute myocardial infarction within 5 months before enrollment, clinically significant uncontrolled hypertension, or any other uncontrolled cardiac condition or concurrent illness that would preclude study conduct and assessment; QT interval corrected by the Fridericia method >480 msec (Grade ≥2); history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-079 formulation (including patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction); history of myelodysplastic syndrome or another malignancy other than MM; clinical signs of central nervous system involvement of MM; or active chronic hepatitis B or C infection, or

active HIV infection. Also excluded are patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance; smoldering myeloma; solitary plasmacytoma; amyloidosis; Waldenström macroglobulinemia or immunoglobulin M myeloma, and patients with positive Coombs tests at screening; for patients in the Combination Cohort (TAK-079–PomDex) only: patient has previously received pomalidomide or has hypersensitivity to thalidomide or lenalidomide.

Endpoints (in order of importance):

Primary:

Phase 1

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).

Phase 2a

- Overall response rate (ORR), defined as the proportion of patients who achieved a partial response (PR) or better during study as defined by IMWG Uniform Response Criteria.

Secondary:

Phase 1

- RP2D based on both safety and efficacy outcomes as a single agent and when added to a backbone regimen of PomDex.
- Summary statistics for the following PK parameters as a single agent and when added to a backbone regimen of PomDex:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-079, as single agent and in combination with PomDex, will be assessed for patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria.
  - Proportion of patients who achieved minimal response (MR), defined as 25% tumor reduction, including in patients with disease measurable by serum FLCs.
- Anti–TAK-079 antibody incidence and characteristics.

Phase 2a

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction, will be evaluated.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date

of the first documented PD.

- PFS, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause.
- OS, defined as the time from the date of the first dose to the date of death due to any cause.
- Time to response, defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

Exploratory:

[redacted]

Statistical Considerations:

The MTD/RP2D will be estimated by a 3+3 dose escalation design using data collected in the dose-escalation phase of the study. After review of the available safety, efficacy, PK, [redacted] data, additional cohorts may be expanded by enrolling additional patients to obtain a more comprehensive assessment of disease response and to further inform selection of the R2PD.

Adverse events will be summarized by treatment group and overall. Categorical variables such as ORR will be tabulated by treatment group and overall. Time to event variables such as DOR and PFS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided.

PK parameters will be summarized as appropriate.

Sample Size Justification:

Phase 1 of the study will follow a 3+3 dose escalation schema.

The selection of the next recommended dose will be determined based on safety, clinical, PK, [redacted] data. Dose-escalation cohorts may be expanded to include additional patients to obtain a more comprehensive assessment of disease response before the phase 2a portion of this study is opened to enrollment. Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 55: 19 patients have been enrolled in dose Escalation Cohort and approximately 36 patients will be enrolled in total in the 2 new cohorts added with amendment 03.

In phase 2a, approximately 48 additional patients will be treated to provide a preliminary estimate of the ORR in two expansion cohorts of patients with RRMM: up to 24 patients with RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

No prospective calculations of statistical power have been made; however, the following table shows the width of the 80% CI, based on the observed ORR in a cohort size of 24 patients, for a range of observed response rates.

[redacted]

[redacted]

3.0 STUDY REFERENCE INFORMATION

Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities (Appendix C). The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

Principal Investigator

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

[redacted]

3.1 List of Abbreviations

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
AML	acute myeloid leukemia
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
[redacted]	[redacted]
BMA	bone marrow aspirate
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form (refers to any media used to collect study data [ie, paper or electronic])
EOI	end of infusion
EOT	end of treatment
FDA	United States Food and Drug Administration
FIH	first-in-human
FLC	free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
Ig	immunoglobulin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group

Abbreviation	Term
IR	infusion reaction
IRB	institutional review board
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAB	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PB	plasmablast
PD	progressive disease; disease progression
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome
PomDex	pomalidomide in combination with dexamethasone
PR	partial response
PT	Preferred Term
QTc	QT interval corrected for heart rate
RBC	red blood cell(s)
REMS	Risk Evaluation and Mitigation Strategy
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SCRS	severe cytokine release syndrome
SOC	System Organ Class
SOE	schedule of events

[redacted]

Abbreviation	Term
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reactions
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration
[redacted]	[redacted]
TTR	time to response
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WOCBP	women of childbearing potential

4.0 INTRODUCTION

4.1 Background

TAK-079 is a fully human antibody of the immunoglobulin G1 (IgG1) subclass, which targets CD38 expressing cells for destruction through multiple mechanisms of action (complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity). TAK-079 treatment results in a rapid depletion of CD38+ leukocytes in the peripheral blood, as observed in nonhuman primate studies and in humans. A number of hematologic tumors express CD38, including multiple myeloma (MM), acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia (CLL), and B-cell non-Hodgkin lymphoma.

MM is a plasma cell-derived malignancy that accounts for approximately 1% of all cancers [1]. It is characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency. The 5-year survival rate of patients with MM is approximately 45% [1]. MM persists as a mostly incurable disease due to its highly complex and diverse cytogenetic and molecular abnormalities [2]. There has been improvement in the outcome for patients with MM in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory drugs (IMiDs) like lenalidomide, but patients who become refractory or are ineligible to receive PIs and IMiDs have a dismal prognosis [3]. In November 2015, the United States Food and Drug Administration (FDA) approved the CD38 antibody daratumumab (DARZALEX; Janssen) for the treatment of MM [4]. Daratumumab was studied in patients who had received at least 3 prior lines of therapy including a PI and an IMiD, or who were double-refractory to these agents. An overall response rate (ORR) of 29% was documented, including a 3% rate of complete response (CR)/stringent complete response (sCR). The main toxicity associated with daratumumab was infusion reactions (IRs), which were severe in some patients. Other common adverse reactions were fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection [5]. Notably, not all patients respond and many patients eventually develop progressive disease (PD) on daratumumab monotherapy [6].

4.2 Findings From Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, PK, and toxicology studies are provided below. More detailed information is provided in the TAK-079 Investigator's Brochure (IB).

[redacted]

[redacted]

Systemic exposures in the 13-week toxicity studies were considered adequate for assessment despite the formation of antidrug antibodies (ADA) observed more frequently at the lower doses, which negatively affected exposures likely via increased clearance. Assessments of local tolerance via either IV or SC dosing routes indicated no significant local injection site liabilities.

[redacted]

Human erythrocytes [7] and platelets [8] express low levels of CD38, and the presence of erythrophagocytosis in the marrow suggests an immune-mediated component. The absence of erythrophagocytosis in the spleen, lymph nodes, and liver suggests that immune-mediated anemia did not result from targeting of mature erythrocytes. In an investigative study, binding of TAK-079 to cynomolgus or human RBCs or platelets from 30 different donors was not detected; however, a more sensitive assay did subsequently detect binding of TAK-079 to CD38+ expressed on human erythrocytes, which is consistent with binding of daratumumab to human RBCs. A mid-to-low level of CD38+ expression is reportedly present on erythrocytes and megakaryocyte erythroid progenitors. This was confirmed as moderate-to-marked membranous TAK-079 positive staining of hematopoietic cells in human bone marrow, which suggests targeting of progenitor cells as the mechanism of anemia and thrombocytopenia.

Collectively, these data support the continued use of TAK-079 in humans.

4.2.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2.2 Preliminary Findings From the Dose Escalation Period of This Study

As of 05 March 2018, 19 patients have been enrolled through the first 4 dose planned cohorts (45, 135, 300, and 600 mg). In this ongoing study, the most common (in >2 patients) treatment-emergent AEs by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) regardless of causality in the total population as of 05 March 2018 are anaemia (n = 5 patients, insomnia, headache, and hypertension (n = 4 patients each), and upper respiratory tract infection, fatigue, and decreased appetite (n = 3 patients each). All AEs have been Grade 1 or 2; 2 events were reported as drug-related Grade 3 AEs (decreased neutrophil count and anemia [in 1 patient each] both of which were transient. No patient experienced dose-limiting toxicities (DLTs), injection site reactions, discontinued TAK-079 due to TEAEs, or died on-study; 2 patients experienced SAEs, none were reported as treatment related (1 event was pretreatment). No patient has been demonstrated to have had CRS symptoms; 1 patient in the 135 mg cohort did report transient facial flushing Cycle 2 Day 1, which the investigator reported as drug related.

In the original phase 1 dose Escalation Cohorts, TAK-079 was given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD. Based on a review of available clinical activity, PK, and pharmacodynamic findings, the dose of TAK-079 as monotherapy in the Confirmation Cohort and when added to PomDex in the Combination Cohort will be 300 mg in the same schedule as follows:

Confirmation Cohort: TAK-079 will be given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD in subsequent cycles.

Combination Cohort: TAK-079 will be given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD in subsequent cycles with PomDex given according to product information (Pomalyst USPI, including Section 14.1).

4.3 Known and Potential Benefits and Risks to Patients With TAK-079

TAK-079 was administered only in healthy human subjects in the first-in-human (FIH) study (TAK-079_101). Only mild or moderate AEs were observed in the FIH study in healthy subjects. Therefore, clinical benefits and risks have not been assessed in the disease setting.

TAK-079 has now been administered to patients with advanced RRMM (TAK-079-1501; this study). Only mild or moderate (Grade 1 or 2) TEAEs were observed as described above.

A summary of findings is discussed in Section 4.3.1. See details for precautions and restrictions in Section 8.10. Additional information regarding potential discomforts and risks from treatment is provided in the TAK-079 IB.

4.3.1 Potential Risks

Based on the mechanism of action of TAK-079, potential AEs may include infusion or injection site reactions, CRS, hematological effects, and infections.

[redacted]

4.3.1.1 Infusion and Injection Site Reactions

IRs are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents aimed at treating hematologic malignancies [5]. IRs are less frequently associated with SC injection of these therapies. The 'true' clinical hypersensitivity reactions, antibody-mediated occur after repeat exposure. Symptoms of hypersensitivity range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Non-anaphylactic clinical hypersensitivity occurs within the first hour; however delayed responses were reported. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, bronchospasm, respiratory distress, and shock [9].

There are limited nonclinical and clinical data to date for TAK-079 (Section 4.2.1). Local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. In the clinical study of healthy subjects (TAK-079_101), an infusion-related reaction was defined as a TEAE occurring within 2 hours of the start of an infusion; there were no IRs in this study, as no allergic or cytokine release reactions were observed within this time period. Mild injection site AEs were reported; AEs were Grade 1 and included primarily erythema or tenderness with palpitation. All injection site reactions resolved within a few days.

In this study (TAK-079-1501) in patients with RRMM at doses up to 600 mg (given with 3 SC injections), no injection site reactions have been reported.

Patients in clinical trials receiving TAK-079 will be carefully monitored for signs and symptoms of infusion and injection site reactions, with appropriate management of these events. Depending on the severity of the reaction, management may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

See additional details for managing infusion and injection site reactions in Section 8.11.1.

4.3.1.2 Cytokine Release Syndrome

CRS represents an important IR often associated with the use of monoclonal antibodies used in anti-inflammatory and antitumor therapies. CRS may occur early in therapy, and often after the first infusion of the drug due to 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 also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting [10,11].

Severe cytokine release syndrome (SCRS) is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumor lysis syndrome such as hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated lactate dehydrogenase, and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with

pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution [10,11]. Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

[redacted]

In the FIH study conducted in healthy human subjects, rarely-observed symptoms consistent with mild CRS were reported particularly at higher doses, and they did not require dose adjustment or interruption. In this study (TAK-079-1501) in patients with RRMM at doses up to 600 mg, 1 transient event on Cycle 2 Day 1 of drug-related flushing in a single patient in the 135 mg cohort could conservatively be a symptom of a systemic infusion reaction; however, no other symptoms have been reported in this or other patients.

Potential occurrence of events associated with CRS will be carefully monitored in patients receiving TAK-079 and managed according to institutional guidelines. Patients who develop SCRS should have dosing interrupted immediately and should receive aggressive symptomatic treatment.

4.3.1.3 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the NOAEL of 0.3 mg/kg. The NOAEL was based on occurrence of thrombocytopenia in 1 of 14 monkeys and is believed to be species specific. In the TAK-079 FIH (TAK-079-101) and RRMM (this study TAK-079-1501) at doses up to 600 mg, no decrease in platelet counts below the lower limit of normal related to TAK-079 were seen (note 1 event of grade 3 thrombocytopenia was reported as related to progression of the underlying advanced myeloma in study TAK-079-1501).

Subjects in clinical studies of TAK-079 should be monitored closely, including testing of hematology parameters throughout this study, as described in Section 9.4.13 and Appendix A.

4.3.1.4 Infections

In a GLP-compliant 13-week toxicology study, bacterial and/or viral infection secondary to immune suppression was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

In the TAK-079 FIH study, mild infections, specifically nasopharyngitis was reported. In the study in patients with RRMM (TAK-079-1501, this study), 4 of 19 patients treated at doses up to 600 mg

[redacted]

reported an AE in the infection and infestation MedDRA System Organ Class (SOC); the most common AE reported was upper respiratory infection (n = 3); all were grade 2 and only 1 was reported as related to study drug.

Subjects will be monitored for any signs and symptoms of infections throughout this clinical study (see Section 8.11.4).

4.3.1.5 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 monoclonal antibody (mAb), the risk of drug-drug interactions is low.

4.3.1.6 ADA Interactions

ADA responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Strong positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeat-dose toxicity studies and at lower doses.

In the single-dose healthy subject study (TAK-079_101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these, 1 subject was treated in the 0.06 mg IV cohort and the remaining 4 subjects were treated with either 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity.

4.3.1.7 Pregnancy and Lactation

TAK-079 has not been administered to women who are pregnant or lactating. Dedicated fertility and embryo-fetal development toxicology studies have not been conducted with TAK-079. However, there were no TAK-079–related changes in organ weights or microscopic findings noted in the male and female reproductive tract of monkeys following administration for up to 13 weeks. Women of childbearing potential (WOCBP) may be enrolled in clinical trials with appropriate precautions to prevent pregnancy (additional details in Section 8.10).

At this stage of development TAK-079 should not be administered to women who are pregnant or breastfeeding.

4.3.1.8 Overdose

TAK-079 has been administered only to healthy subjects in the FIH study. To date, there is no experience with overdose. If an overdose does occur, close monitoring and supportive treatment as medically required are recommended.

4.3.2 Overall Benefit and Risk Assessment for This Study

The overall clinical benefits and risks of TAK-079 have not been determined.

Based on the mechanism of action of TAK-079, nonclinical data to date, as well as some exposure in healthy human subjects, possible AEs of TAK-079 include but are not limited to infusion and injection site reactions, CRS, hypersensitivity reactions, changes in hematologic parameters, and infections. Patients will be monitored closely for these risks in this clinical study.

The emerging preliminary safety profile, as detailed above and in the current Investigator Brochure, indicate that TAK-079 is generally well tolerated with manageable and reversible AEs. The potential toxicities can be managed by clinical monitoring and standard medical interventions. It is possible that TAK-079 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-079, patients will be carefully monitored closely for signs and symptoms of systemic and injection site reactions with appropriate management of these events. Guidance for the management of AEs are provided in Section 8.11. Depending on the severity of the reaction, drug dosage can be reduced by dose modification (holding or delaying) of the scheduled treatment within a cycle as provided in Section 8.6, and may include discontinuation of TAK-079.

In patients with advanced RRMM, TAK-079 has shown early signs of antitumor activity as evidenced by at least 50% reduction in disease burden in some patients and prolonged disease stabilization in others. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of TAK-079.

4.4 Rationale for the Proposed Study

Although multiple therapies are available for patients with MM, this disease remains incurable; thus, significant unmet medical need exists for this patient population. Frequent relapses highlight a need for new therapies for patients in whom prior treatments have failed.

TAK-079 binds to unique amino acids of CD38 and possesses a different binding profile than the approved cytolytic anti-CD38 therapeutic antibody daratumumab.

In the FIH study (TAK-079_101), TAK-079 demonstrated pharmacodynamic effects (ie, cytolysis of NK cells and PBs) following single-dose administration, with no unexpected and unwanted clinical or hematologic effects observed. For example, NK cells were reduced >90% from baseline levels in all healthy subjects receiving a single 0.06 mg/kg IV dose of TAK-079 and exhibited a mean C_{max} of 0.1 ug/mL (TAK-079_101). Comparable depletion of NK cells by daratumumab administered IV to a population of patients with refractory MM [12] required doses of >24 mg/kg and a mean C_{max} of >500 ug/mL [13,14]. Consequently, TAK-079 may be significantly more efficient at eliminating target cells in patients, which could manifest as higher activity on tumor cells (ie, activity at lower doses, low-volume SC administration, and less frequent administration), including activity on daratumumab-refractory tumors. The potential activity of TAK-079 should therefore be investigated in patients with relapsed and/or refractory multiple myeloma (RRMM).

4.4.1 Rationale for the Starting Dose of TAK-079

In the FIH study (TAK-079_101), TAK-079 was well tolerated after SC administration of single-doses ranging from 0.03 to 0.6 mg/kg.

[redacted]

To avoid unnecessary exposure of patients to sub-therapeutic doses while preserving safety, the starting dose for this study in patients with RRMM will be 45 mg, the fixed-dose equivalent of 0.6 mg/kg (assuming a body weight of 75 kg), which was the highest SC dose administered in Study TAK-079_101. The 0.6 mg/kg dose was well tolerated in healthy human subjects in Study TAK-079_101 and demonstrated >90% depletion of peripheral blood PBs, a surrogate for myeloma cells in each subject (n = 6).

TAK-079 is a mAb targeting CD38, which is a cell surface molecule that is constitutively expressed on plasma cells, PBs, and NK cells, and is induced on activated T cells and B cells [15]. Therefore, the anticipated elimination routes for TAK-079 are via proteolytic catabolism and intracellular degradation after binding to its target. Both of these clearance mechanisms are not thought to be significantly influenced by body weight. Additionally, the distribution volume of mAbs is generally limited to the volume of the blood and extracellular fluids, such that body composition is a less important determinant of distribution volume as compared with small molecule drugs [16]. For these reasons, body weight is not expected to have a clinically significant effect on the disposition of TAK-079, thereby supporting the investigation of fixed-dose administration.

The 45 mg starting dose of TAK-079 will be tested in 3 patients with RRMM to assess the safety and tolerability of TAK-079 after multiple dose administration. TAK-079 will be administered using the same dosing schedule as the anti-CD38 antibody, daratumumab, which is approved for the treatment of patients with MM [5]. Specifically, TAK-079 will be administered once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), then once every 4 weeks until the patient experiences PD, unacceptable toxicities, or withdrawal due to other reasons. The subsequent planned dose levels are 135, 300, 600, 1200, and 1800 mg.

Escalation to a subsequent cohort may take place after the treatment in the first cycle of the previous (sequential) cohort has completed.

Additional details for dose escalation are provided in Section 8.3.

The dose used in the Confirmation Cohort and the Combination Cohorts is the expected RP2D from the dose Escalation Cohorts, based on preliminary PK and PD results from the dose Escalation Cohort.

Relevant to the Combination Cohort, lenalidomide is established therapy in NDMM [17,18] therefore patients for whom lenalidomide is no longer a treatment option, because of previous exposure, intolerance, or are refractory to lenalidomide, represent a clinically relevant population with unmet need. Nonclinical studies demonstrate that pomalidomide inhibits proliferation of lenalidomide-resistant cells [19]. Clinically, PomDex, an all oral regimen, is approved for patients who have previously received lenalidomide [20]. Adding an anti-CD38 monoclonal antibody to it, especially one that is given SC, could be beneficial and convenient to patients as compared with IV administered anti-CD38 monoclonal antibodies. PomDex will be given at the dose and schedule recommended in the product information (Pomalyst USPI including Section 14.1) while TAK-079 will be given at the RP2D in the revised schedule described in Section 6.1.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

Phase 1

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy and when combined with a backbone regimen of PomDex in patients with RRMM.

Phase 2a

The primary objective of the phase 2a portion of the study is to provide a preliminary evaluation of the clinical activity of TAK-079 monotherapy in patients with RRMM.

5.1.2 Secondary Objectives

Phase 1

The phase 1 secondary objectives are:

- To investigate a potential MTD/RP2D of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To evaluate the immunogenicity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To characterize the PK of TAK-079 as a single agent and when added to a backbone regimen of PomDex.
- To provide a preliminary evaluation of the clinical activity of TAK-079 as a single agent and when added to a backbone regimen of PomDex.

Phase 2a

The phase 2a secondary objectives are:

- To further evaluate safety at the MTD/RP2D.
- To provide a preliminary evaluation of time-to-event measures.
- To further evaluate the immunogenicity of TAK-079.
- To further characterize the PK of TAK-079.

5.1.3 Exploratory Objectives

[redacted]

[redacted]

5.2 Endpoints

5.2.1 Phase 1 Primary Endpoints

The primary endpoints for phase 1 are:

- The number of patients with TEAEs overall and per dose level.
- Patients with DLTs at each dose level.
- Patients with Grade ≥3 TEAEs.
- Patients with SAEs.
- Patients who discontinue because of TEAEs.
- Patients with dose modifications (delays, interruptions, dose reductions).

5.2.2 Phase 2a Primary Endpoint

The primary endpoint for phase 2a is:

- ORR, defined as the proportion of patients who achieved a partial response (PR) or better during the study as defined by International Myeloma Working Group (IMWG) Uniform Response Criteria [21,22].

5.2.3 Phase 1 Secondary Endpoints

The secondary endpoints for phase 1 are:

- RP2D based on both safety and efficacy outcomes as a single agent and when added to a backbone regimen of PomDex.
- Summary statistics for the following PK parameters as a single agent and when added to a backbone regimen of PomDex:
  - Maximum observed concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).

[redacted]

  - Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).

- Preliminary evaluation of antitumor activity of TAK-079, as single agent and in combination with PomDex, will be assessed for patients with MM by measuring:
  - ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria ([21,22]; Appendix E).
  - Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction, including in patients with disease measurable by serum free light chains (FLCs) ([21,22]; Appendix E).
- Anti–TAK-079 antibody incidence and characteristics.

5.2.4 Phase 2a Secondary Endpoints

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- Progression-free survival (PFS), defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause ([21,22]; Appendix E).
- Overall survival (OS), defined as the time from the date of first dose to the date of death due to any cause.
- Time to response (TTR), defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

5.2.5 Exploratory Endpoints

[redacted]

[redacted]

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a multicenter, dose-escalation, open-label, single-arm, phase 1/2a study designed to determine the safety, tolerability, efficacy, PK, and immunogenicity of TAK-079 monotherapy in patients with RRMM, and to provide a preliminary assessment of its activity against MM.

The phase 1 portion of the study will evaluate administration of single agent TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs from medical review of vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, review of concomitant medications, dose modifications, and treatment discontinuations.

MM is a heterogenous disease requiring treatments across multiple lines of therapy despite recent advances. The pace of MM treatment has been rapid in recent years and even with a shift towards triplet regimens from doublet regimens, patients are still relapsing from, ineligible for, or intolerant to such combinations. Further the treatment paradigm is fragmented due to patient factors as well as disease factors and acceptance of recently approved regimens is gaining but remains variable. Therefore, this study will continue to evaluate patients with relapsed or refractory disease, including those who have not progressed following daratumumab, in an effort to more fully understand the activity of TAK-079 in patients who represent the highly heterogeneous population seen in current clinical practice. Before enrolling into the phase 2a phase of the study, additional patients will be enrolled in a dose Confirmatory Cohort to better understand the safety and clinical activity of the TAK-079 RP2D based on preliminary PK/[redacted] data.

More patients now receive combinations of lenalidomide, bortezomib, dexamethasone with or without daratumumab as first-line treatment, yet their disease still progresses. Most develop lenalidomide-resistant disease; thus, alternatives to lenalidomide are required in later lines of therapy. Pomalidomide with dexamethasone is approved for patients following therapy with lenalidomide and a proteasome inhibitor; however, the duration of response is short (7.4 months) [20]. Evidence is emerging that adding an IV administered anti-CD38 agent to PomDex can help prolong response duration [23]. TAK-079, a SC administered anti-CD38 monoclonal antibody, is showing early signs of antimyeloma activity as a monotherapy in patients with advanced RRMM. Adding TAK-079 to the PomDex backbone could provide benefit to patients both in terms of improved antimyeloma activity over each agent alone, and would be more convenient to patients as compared with administration of IV administered anti-CD38 agents (ie, a TAK-079, a SC agent, added to the all oral PomDex regimen). Hence a new cohort will open to evaluate this combination. Information about the dose, safety, and activity of TAK-079 added to a standard backbone regimen of PomDex in patients with RRMM who have received at least 2 prior therapies and have demonstrated PD on or within 60 days of the completion of the last therapy will be collected.

[redacted]

The preliminary efficacy of TAK-079, as monotherapy and when added to PomDex, will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [21,22]). In addition, the efficacy of TAK-079 will be assessed by measuring MR, PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the phase 1 Dose Escalation phase, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or withdraw due to other reasons (see Section 6.3).

In the phase 1 Confirmation Cohort Phase, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD.

- In this cohort, up to 6 patients that are refractory to an anti-CD38 agent will be enrolled.
- Further in this cohort, approximately 12 patients that have RRMM disease (per prior therapy inclusion criteria Section 7.0) and are naïve to an anti-CD38 agent will be enrolled.

In the Combination Cohort, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1).

- In this cohort, up to 6 patients will initially be enrolled. Safety in Cycle 1 will be reviewed in accordance with DLT definitions in Section 8.2.
- If 0 of 6 or 1 of 6 patients develop a DLT an additional 12 patients will be tested at the initial dose of TAK-079 [6 patients that are naïve to a prior anti-CD38 agent and 6 patients that have been exposed to a prior anti-CD38 agent], for an overall total of 18 patients.
- If 2 of 6 patients develop DLTs all available data will be reviewed before making decisions about study conduct (See details in Section 8.5).

The Confirmation Cohort and the Combination Cohort may start in parallel and will run independently.

All cohorts will consist of the following phases/periods: screening, treatment, and follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing):
- Original dose Escalation Cohort: once-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.

[redacted]

- Dose Confirmation Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD.
- Combination Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1 describing dexamethasone dosing).
- Follow-up period (end of treatment [EOT] visit): Patients who discontinue study treatment will be followed for approximately 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks from the EOT visit until PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first. Patients who discontinue for PD will be followed for OS after the EOT visit. All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

In phase 1, approximately 6 doses will be evaluated in ascending cohorts of 3 to 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose (300 mg); 12 patients will have been previously treated (see Section 7.0), up to 6 patients will have been previously treated and are refractory to an anti-CD38 therapy (see Section 7.0). In the Combination Cohort, approximately 18 patients will be enrolled who have received prior therapy and have demonstrated PD on or within 60 days of completion of the last therapy, note Section 7.0.

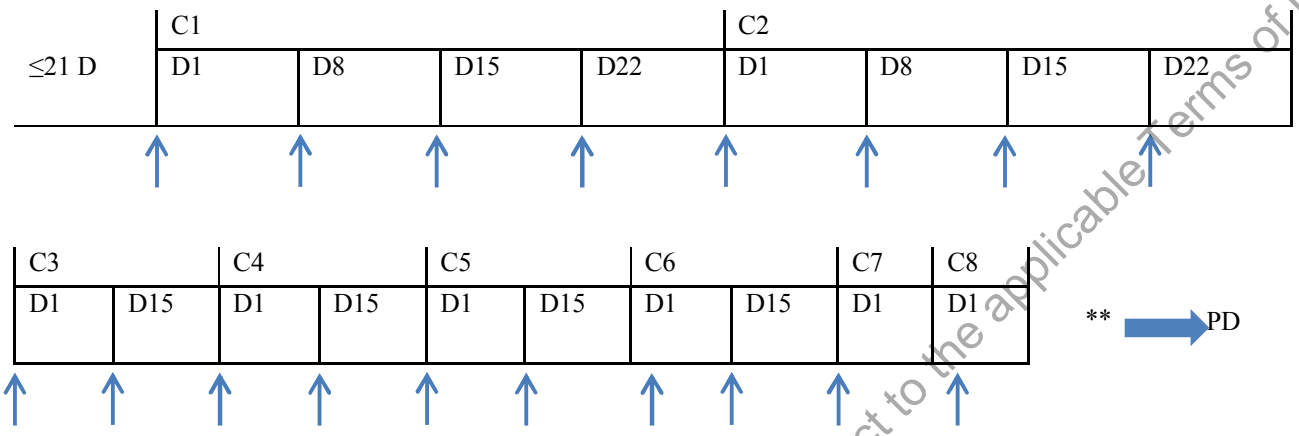
It is expected that approximately 100 patients will be enrolled in total for the phase 1 cohorts and phase 2a combined.

Study procedures and assessments, with their time points, are shown in Appendix A. The study schematic diagram is shown in Figure 6.a.

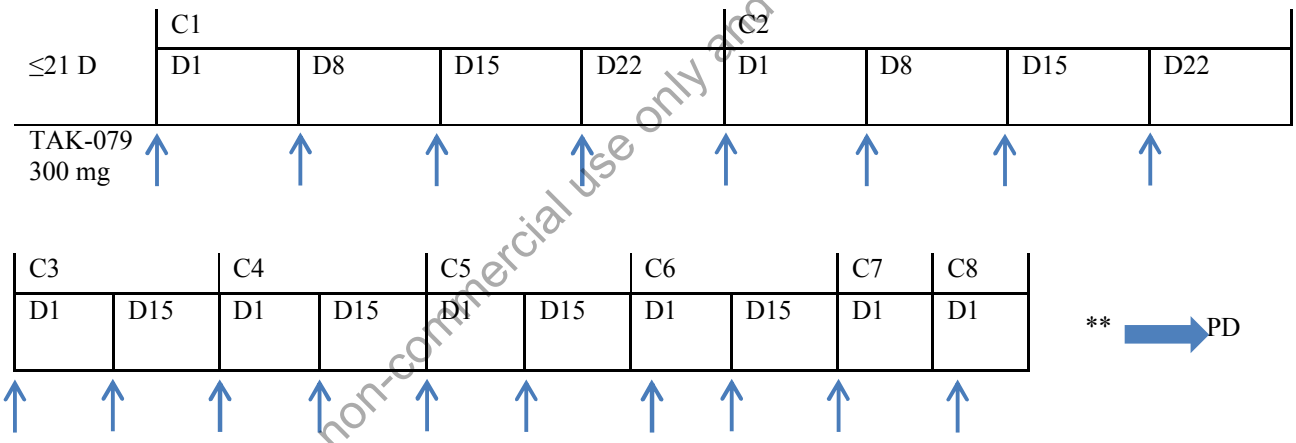
[redacted]

Figure 6.a Overall Study Schematic Diagram

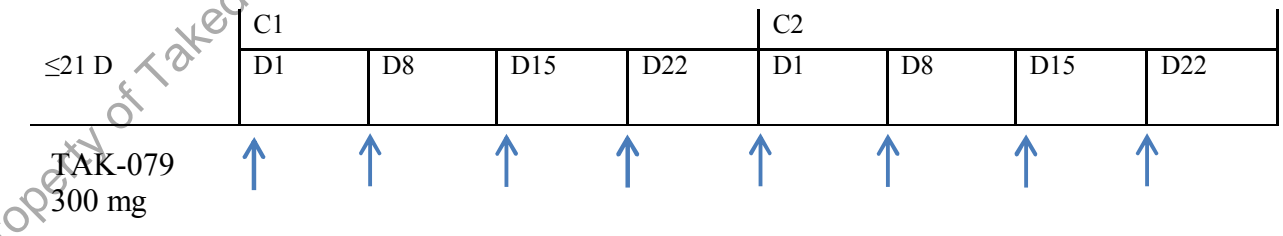
Treatment Cycle: original phase 1 dose Escalation Cohort



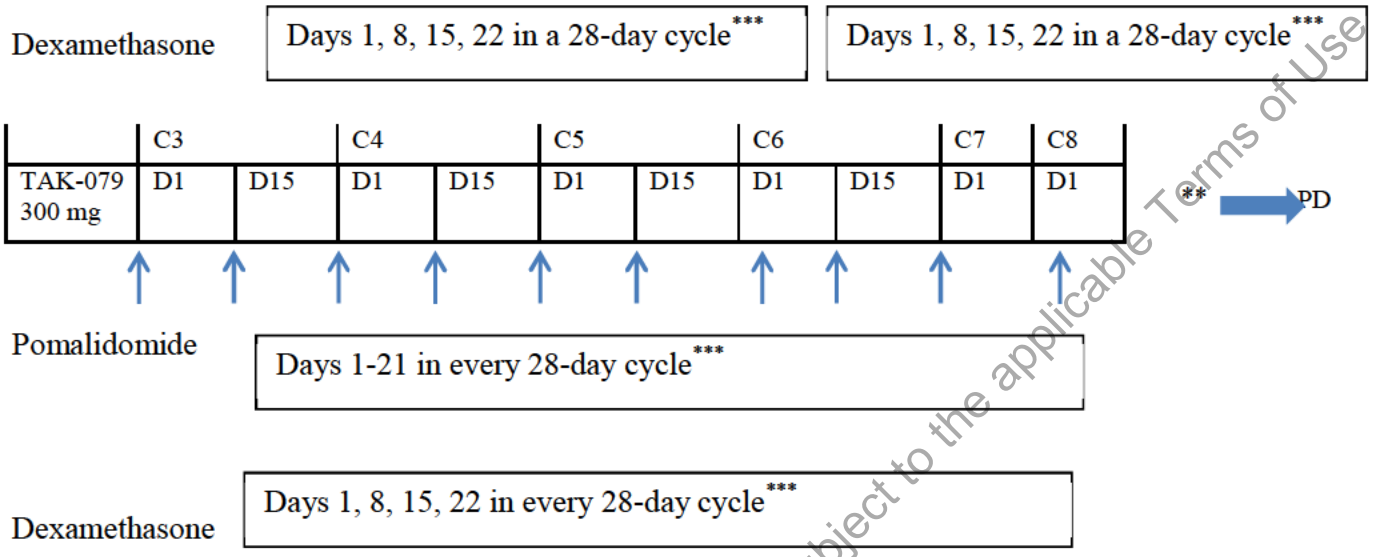
Treatment Cycle: phase 1 dose Confirmation Cohort



Treatment Cycle: new Combination Cohort



[redacted]



C: Cycle; D: Day; PD: progressive disease; R2PD: recommended phase 2 dose; SC: subcutaneous.
Dose Escalation: 45, 135, 300, 600, 1200, and 1800 mg.
Cohorts in phase 1 may be expanded to further inform selection of the RP2D.
The RP2D determined in phase 1 will be further assessed in approximately 48 patients in phase 2a.
* For dose levels where multiple SC injections are needed to administer the full prescribed dose, the Cycle 1 Day 1 dose SC injections will be given with a 30 minute interval in between each SC injection. Thereafter, if there are not clinically significant IRs, the SC injections may be given together without the waiting period.

** → = dosing every 28 days until disease progression.
↑ = TAK-079 dose.

***Dose Confirmation and Combination cohort the dose of TAK-079 is 300 mg. In the Combination cohort the dose of pomalidomide and dexamethasone is per product labeling.

6.2 Number of Patients

For phase 1, approximately 55 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately 48 patients are planned.

In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose and schedule: 12 patients with RRMM that is anti-CD38 naive and up to 6 patients with RRMM that is refractory to an anti-CD38 therapy. In the Combination Cohort, approximately 18 patients with RRMM that has been previously treated with at least 2 prior therapies and that is refractory to the last therapy will be enrolled.

In phase 2a, approximately 48 additional patients will be treated to provide a preliminary estimate of the ORR in 2 expansion cohorts of patients with RRMM: up to 24 patients with RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an anti-CD38 therapy phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

[redacted]

Details on the definition of evaluable patients and sample size are given in Section 13.1.

The study is planned to be conducted in the United States in approximately 7 investigational centers, although the sponsor may add more centers depending on enrollment rates.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-079 until they experience PD as defined by IMWG criteria [21,22] (Appendix E), unacceptable toxicity, or any other discontinuation criterion is met (see Section 8.6.3 and Section 9.7). In the combination cohort, additionally patients will receive PomDex until they experience PD as defined by IMWG criteria. The maximum duration of treatment is expected to be 12 months for patients receiving monotherapy and approximately 18 months for patients in the combination cohort; however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment with the explicit approval of the sponsor's study clinician (see Section 6.3.5 for Posttrial Access).

Patients will be evaluated 30±7 days after the last dose of TAK-079 (follow-up visit) or before initiating subsequent systemic anticancer therapy, for detection of any delayed TEAEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the clinical study report may be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with single agent TAK-079, 18 months of combination therapy, or after the last patient completes the EOT visit if the sponsor terminates the study earlier (Table 6.a).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

[redacted]

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint		Definition	Maximum Time Frame From Final Clinical Study Report
Phase 1			
Primary:	Number of patients with TEAEs overall and per dose level: patients with DLTs at each dose level; patients with Grade ≥3 TEAEs; patients with SAEs; patients who discontinue because of TEAEs; patients with dose modifications (delays interruptions, or dose reductions)	Includes assessments for patients with DLTs, Grade ≥3 TEAEs, SAEs, discontinuations because of TEAEs, and dose modifications	1 year
Secondary:	Summary statistics for PK parameters: C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary:	Preliminary evaluation of antitumor activity of TAK-079: MR	Proportion of patients who achieved a minimal response, defined as 25% tumor reduction. See Section13.1.3.	1 year
Secondary:	Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year

ADA: antidrug antibody; C_{max}: maximum observed concentration; DLT: dose-limiting toxicity; IMWG: International Myeloma Working Group; MR: minimal response; ORR: overall response rate; PK: pharmacokinetics; PR: partial response; SAE: serious adverse event; TEAE: treatment-emergent adverse event; t_{max}: time of first occurrence of maximum observed concentration.

[redacted]

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

Endpoint	Definition	Maximum Time Frame From Final Clinical Study Report
Phase 2a		
Primary: ORR	Proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria. See Section 13.1.3.	1 year
Secondary: DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification and treatment discontinuation.	Includes assessments for patients with DLTs and other TEAEs, dose modifications and treatment discontinuations.	1 year
Secondary: Summary statistics for PK parameters of C_{max}, t_{max}, and AUC_{last}.	Summary statistics for maximum observed concentration, time to first occurrence of C_{max}, and area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}). See Section 13.1.4.	1 year
Secondary: Anti–TAK-079 antibody incidence and characteristics	Assessment of ADA antibodies following treatment. See Section 13.1.6.	1 year
Secondary: MR	Proportion of patients who achieved MR, defined as 25% tumor reduction. See Section 9.4.14 and 13.1.3.	1 year
Secondary: DOR	Time from the date of the first documentation of response to the date of the first documented PD. See Section 13.1.3.	1 year
Secondary: PFS	Time from the date of the first dose until the earliest date of PD, or the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: OS	Defined as the time from the date of first dose to the date of death due to any cause. See Section 13.1.3.	1 year
Secondary: TTR	Time from the date of the first dose to the date of the first documentation of response (PR or better). See Section 13.1.3.	1 year

DLT: dose-limiting toxicity; DOR: duration of response; IMWG: International Myeloma Working Group; MR: minimal response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TTR: time to response.

6.3.4 Total Study Duration

The final analyses for the clinical study report may be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with single agent TAK-079, 18

[redacted]

months of combination therapy, or after the last patient completes the EOT visit if the sponsor terminates the study earlier.

It is anticipated that this study will last for approximately 42 months (3.5 years).

6.3.5 Posttrial Access

At the conclusion or termination of the study or termination of a treatment arm in the study, if patients are, in the opinion of the investigator and confirmed by the sponsor, experiencing a clinically important benefit, TAK-079 treatment may be continued in this study or another extension or rollover study, if and when such a study is made available, upon request by the investigator and agreement by the sponsor. Continued access to TAK-079 for participants will be terminated for those individuals who no longer benefit from TAK-079, the benefit-risk no longer favors the individual, if TAK-079 becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in areas where marketing authorization has been rejected, the development of TAK-079 has been suspended or stopped by the sponsor, or TAK-079 can no longer be supplied. Only for patients enrolled into the Combination Cohort, the backbone agents ongoing at this time will continue to be procured by the site from commercial sources.

[redacted]

7.0 STUDY POPULATION

Phase 1 dose Confirmation Cohort: Adult patients with relapsed and/or refractory multiple myeloma who have been previously treated with at least a PI, an IMiD, and a steroid. Patients should have refractory disease or be intolerant to at least 1 PI and at least 1 IMiD, and they should have either received 3 or more prior therapies or received at least 2 prior therapies if one of those therapies included a combination of a PI and an IMiD. Patients who have had a previous autologous stem cell transplant will have additionally been exposed to an alkylating agent; however, patients who have not had a previous autologous stem cell transplant may not have been exposed to an alkylating agent per standard practice. Up to 6 patients will be refractory to an anti-CD38 agent and approximately 12 patients in this cohort should be anti-CD38 naïve.

Combination Cohort: Adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated PD on or within 60 days of the completion of the last therapy. The first 6 patients enrolled may be either naïve to a prior anti-CD38 antibody or may have been exposed to one previously (if exposed note washout period in Table 7.a). Once safety data have been reviewed, the following patients enrolled at the RP2D/MTD will be: naïve to a prior anti-CD38 monoclonal antibody (approximately 6 patients) or exposed to a prior anti-CD38 monoclonal antibody (approximately 6 patients; note washout period in Table 7.a).

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. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 [24].
3. Patient has received the final dose of any of the following treatments/procedures within the specified minimum intervals before the first dose of TAK-079 (Table 7.a):

Table 7.a Required Washout Periods for Previous Treatments or Procedures Prior to Administration of TAK-079

Previous Treatment or Procedure	Washout Period
Myeloma-specific therapy	14 days
Antibody therapy (including anti-CD38)	180 days
Corticosteroid therapy (a)	7 days
Autologous transplantation	90 days
Radiation therapy (b)	14 days
Major surgery	14 days

(a) Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent) is allowed.
(b) Prophylactic "spot" radiation for areas of pain is permitted.

4. Patient has adequate organ function as determined by the following laboratory values (Table 7.b):

Table 7.b Laboratory Criteria for Determining Adequate Organ Function for Study TAK-079-1501 Eligibility

Laboratory Parameter	Acceptable Laboratory Criteria
Absolute neutrophil count (a)	≥1000/mm^3 (≥1.0×10^9/L); ≥750/mm^3 (≥0.75×10^9/L) maybe acceptable for patients with >50% of plasma cells in bone marrow after discussion with sponsor
Platelets (a)	≥75,000/mm^3 (≥75×10^9/L); a 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
Hemoglobin	≥7.5 g/dL (it is not permissible to transfuse a subject to reach this level)
Creatinine clearance	≥30 mL/min (Cockcroft-Gault formula)
Total serum bilirubin	≤1.5×ULN; except for patients with Gilbert's syndrome in whom direct bilirubin should be <2.0×ULN
Liver transaminases (ALT/AST)	≤2.5×ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of the normal range.
(a) Without ongoing growth factor or transfusion support for at least 1 week before Day 1.

5. Female patients who:
   - Are WOCBP must not be pregnant or lactating.
   - 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 at least 90 days or 5 half-lives after the last dose of study drug, whichever time period is longest (See Section 8.10), OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
   - Patients enrolling in the Combination Cohort (TAK-079–PomDex) only must adhere to the Pomalyst REMS requirements per the product label.
6. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug (See Section 8.10), OR

[redacted]

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.
- Patients enrolling in the Combination Cohort (TAK-079–PomDex) only must adhere to the Pomalyst REMS requirements per the product label.

7. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
8. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.
9. Patients in the Combination Cohort (TAK-079–PomDex) only must be able to take concurrent prophylactic anticoagulation per standard clinical practice as directed by the investigator and the Pomalyst product information.
10. Documentation of RRMM as defined by the IMWG criteria (Appendix E; [21,22]).
11. For patients with MM, 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 FLC assay result with involved FLC level ≥10 mg/dL (≥100 mg/L), provided serum FLC ratio is abnormal.
12. Prior therapy, patients should meet all the following criteria:

    Patients in the dose Escalation Cohort (escalation phase) and patients in the dose Confirmation Cohort;

    - Patient should be previously treated with at least a PI, an IMiD, and a steroid. Note: Patients who have had a previous autologous stem cell transplant will have additionally been exposed to an alkylating agent; however, patient who have not had a previous autologous stem cell transplant may not have been exposed to an alkylating agent per standard practice.
    - Patient should be refractory or intolerant to at least 1 PI and at least 1 IMiD.
    - Patient should either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMiD.

- In phase 1, previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required. [Patients in the dose Escalation Cohort]
- In phase 1 dose Confirmation Cohort, 2 subgroups will be enrolled: up to 6 patients will be enrolled that meet above prior therapy criteria and are refractory at any time to at least 1 anti-CD38 agent and approximately 12 patients will be enrolled that meet above prior therapy criteria but are anti-CD 38 naïve.

Patients in the Combination Cohort (TAK-079 added to PomDex cohort only):

- Patients have undergone prior therapy with ≥2 prior anti-myeloma therapies (line of therapy defined below).
- Patient has either relapsed or relapsed and refractory disease. Should have progressed on or within 60 days of completing the last anti-myeloma therapy (refractory defined below).

13. In the phase 2a portion of the study, up to 2 cohorts of patients with RRMM may be enrolled: 1 that is refractory to at least 1 anti-CD38 mAb therapy at any time during treatment and 1 that is naïve to daratumumab. Available safety and efficacy data will be used to make decisions about the patient cohorts to be enrolled in the phase 2a portion. The final decision on the phase 2a cohorts will be made by sponsor representatives following review of all available data considering stopping rule thresholds. (see Section 13.1.7)

NOTE:

- Refractory is defined as less than a 25% reduction in M-protein (response of stable disease during prior therapy) or PD during treatment or within 60 days after last dose of prior therapy.
- A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of PD, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease [21].

7.2 Exclusion Criteria

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

1. Sensory or motor neuropathy of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≥3 [25].
2. Patients who have received allogeneic stem cell transplant.
3. Patients who have received anti-CD38 antibody therapy and do not fulfill a 180-day washout period before receiving TAK-079.

[redacted]

4. Not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE Grade ≤1 or baseline, excluding alopecia.
5. Congestive heart failure (New York Heart Association) Grade ≥II; cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.
6. History of acute myocardial infarction within 5 months before enrollment or ECG abnormalities during the screening period that are deemed medically relevant by the investigator.
7. QT interval corrected by the Fridericia method >480 msec (Grade ≥2).
8. Concurrent illness that would preclude study conduct and assessment including, but not limited to, uncontrolled medical conditions, uncontrolled systemic or body organ active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease such as severe chronic obstructive pulmonary disease [COPD] with forced expiratory volume <80%, or persistent asthma, pulmonary fibrosis, and history of symptomatic bronchospasm), inflammatory bowel disease, ongoing symptomatic pneumonitis, alcoholic liver disease, or primary biliary cirrhosis.
9. History of stroke or intracranial hemorrhage within 12 months of first dose of study drug; patients requiring anticoagulation therapy for any indication should be discussed with the medical monitor before screening.
10. Active autoimmune disease including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or any chronic condition requiring a higher corticosteroid systemic equivalent than prednisone 10 mg daily. Higher doses of corticosteroids prescribed for any indication must be stopped 7 days prior to first dose of study drug; exceptions may be made for corticosteroids prescribed specifically for management of MM symptoms after discussion with the medical monitor.
11. History of myelodysplastic syndrome or another malignancy other than MM, except for the following: any malignancy that has been in complete remission for ≥3 years, adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, or asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year before the start of study therapy.
12. Clinical signs of CNS involvement of MM.
13. Female patients who are pregnant with a positive serum pregnancy test or lactating during the screening period, or a positive urine pregnancy test on Day 1 before the first dose of study drug, if applicable.

14. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
15. Active chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or active HIV infection.
16. History of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation. This includes patients who were previously discontinued from an anti-CD38 treatment due to an infusion-related reaction.
17. The patient is currently participating in another antimyeloma clinical study, or has participated in another investigational clinical trial within the 4 weeks prior to first dose of study drug.
18. Patients who are not able and/or willing to comply with the study requirements, rules, and procedures.
19. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, or IgM myeloma.
20. Patients with positive Coombs tests at screening.
21. For patients in the Combination Cohort (TAK-079–PomDex) only: patient has previously received pomalidomide or has hypersensitivity to thalidomide or lenalidomide.

[redacted]

8.0 STUDY DRUG

8.1 Study Drug Administration

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

8.1.1 Predose and Postdose Medication

Premedications are required in phase 1 and phase 2a.

The clinical site is responsible for sourcing any premedications outlined in the protocol.

8.1.1.1 Predose Medication: Phase 1 Dose Escalation and Dose Confirmation Cohorts

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor).

NOTE: For any patients with a history of COPD, consider prescribing postinfusion medications, such as short- and long-acting bronchodilators, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional inhaled postinfusion medications may be discontinued.

8.1.1.2 Predose Medications: Phase 1 Combination Cohort (TAK-079–PomDex) Only

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration on each dosing day:

- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor).

NOTE: For any patients with a history of COPD, consider prescribing postinfusion medications, such as short- and long-acting bronchodilators, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional inhaled postinfusion medications may be discontinued.

[redacted]

8.1.1.3 Postdose Medications (All Patients)

Postinjection site care: Apply 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).

Patients may receive low-dose methylprednisolone (<20 mg) for the prevention of delayed injection-related reaction as clinically indicated after an injection.

8.1.2 TAK-079 Formulation and Administration

The strength of the TAK-079 drug product for SC use in the current study (TAK-079-1501) is 100 mg TAK-079 in 1 mL (100 mg/mL). The drug product is supplied in clear borosilicate glass vials (see additional details in Section 8.13).

After patients have received premedication treatment, TAK-079 doses will be administered with syringes as SC injections up to a maximum volume of 2 mL per injection (ie, 200 mg/2 mL). For dose levels where multiple SC injections are needed to administer the full prescribed dose (ie, 300 mg dose and above), the Cycle 1 Day 1 dose will be administered by giving each SC injection 30 minutes apart until the full scheduled dose has been administered. On all drug administration days after Cycle 1 Day 1, if the patient did not have a clinically significant IR per the investigator, the SC injections can be given at the at the same time without a waiting period.

When patients are to receive multiple SC injections, 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.

Refer to the Pharmacy Manual for detailed instructions regarding preparation of each dose.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [25]. These criteria are provided in the Study Manual. DLTs will be defined as any of the following events regardless of relationship, except those events that are clearly due to extraneous causes.

- Grade 4 laboratory abnormalities, except those events that are clearly due to extraneous causes, will be defined as a DLT.
- Nonhematologic TEAEs of NCI CTCAE Grade ≥3, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs (see Section 10.2 for relatedness guidance), with the following exceptions:
  - Grade 3 nausea/vomiting that can be managed subsequently with antiemetics (Grade 3 nausea or vomiting that persists beyond 48 hours with or without appropriate medical intervention will be considered a DLT).
  - Grade 3 fatigue lasting less than 3 days (approximately 72 hours).

  - Grade 3 elevation of alanine aminotransferase or aspartate aminotransferase that resolves to Grade ≤1 or baseline within 7 days.
  - Grade 3 IR that responds to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids), without recurrence of Grade 3 symptoms. See Section 8.11.1 for handling of IRs with systemic signs and symptoms.

- Hematologic TEAEs of NCI CTCAE Grade ≥4, except those events that are clearly due to extraneous causes, and occurring during the first cycle will be considered DLTs, with the following exceptions:
  - Grade ≥3 hemolysis, except those events that are clearly due to extraneous causes (eg, negative direct Coombs test), will be included in the definition of DLT.
  - Grade ≥3 low platelet count with clinically meaningful bleeding, defined as a blood loss of >100 cc or the requirement of a blood transfusion, will be included in the definition of DLT.
- An incomplete recovery from treatment-related toxicity causing a >2-week delay in the next scheduled injection before the initiation of Cycle 2 will be considered a DLT.

For the purpose of dose escalation, DLTs are those events meeting the criteria above that occur before Cycle 2 Day 1 administration. TEAEs meeting DLT definitions occurring in later cycles will determine the suitability of the MTD as the RP2D.

Patients who experience a DLT should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort; such patients will not count as a patient in that lower dose cohort for escalation decisions.

In phase 1, patients who do not receive 4 full doses of TAK-079 within the 28-day (±2) treatment window or the Day 29 (ie, Cycle 2 Day 1) assessment for reasons other than a DLT will be replaced. Patients experiencing a DLT should not be replaced.

Dose and schedule modifications for toxicity are described in Section 8.6.

8.3 Dose-Escalation Design and Criteria

8.3.1 Dose Levels

Patients will be enrolled in cohorts of 3 to 6, following a 3+3 dose escalation design.

Phase 1

TAK-079 injections will be escalated as follows:

- 45 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

[redacted]

- 135 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 300 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 600 mg, once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1200 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.
- 1800 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD, unacceptable toxicities, or withdrawal due to other reasons.

Cohorts may be expanded by enrolling additional patients to obtain more comprehensive assessment of disease response and to further inform selection of the RP2D.

[redacted]

Phase 2a

In the absence of DLT, the dose that will be administered in the subsequent phase 2a portion of the study will be based upon a comprehensive review of available safety, efficacy, PK, [redacted] information from the phase 1 portion of the study. Also note Section 13.1.7 for phase 2a safety review.

8.3.2 Escalation Schema

A 3+3 dose escalation schema will be used to inform dose escalation decisions and MTD/RP2D estimation. Initially, 3 patients will be enrolled at the starting dose level.

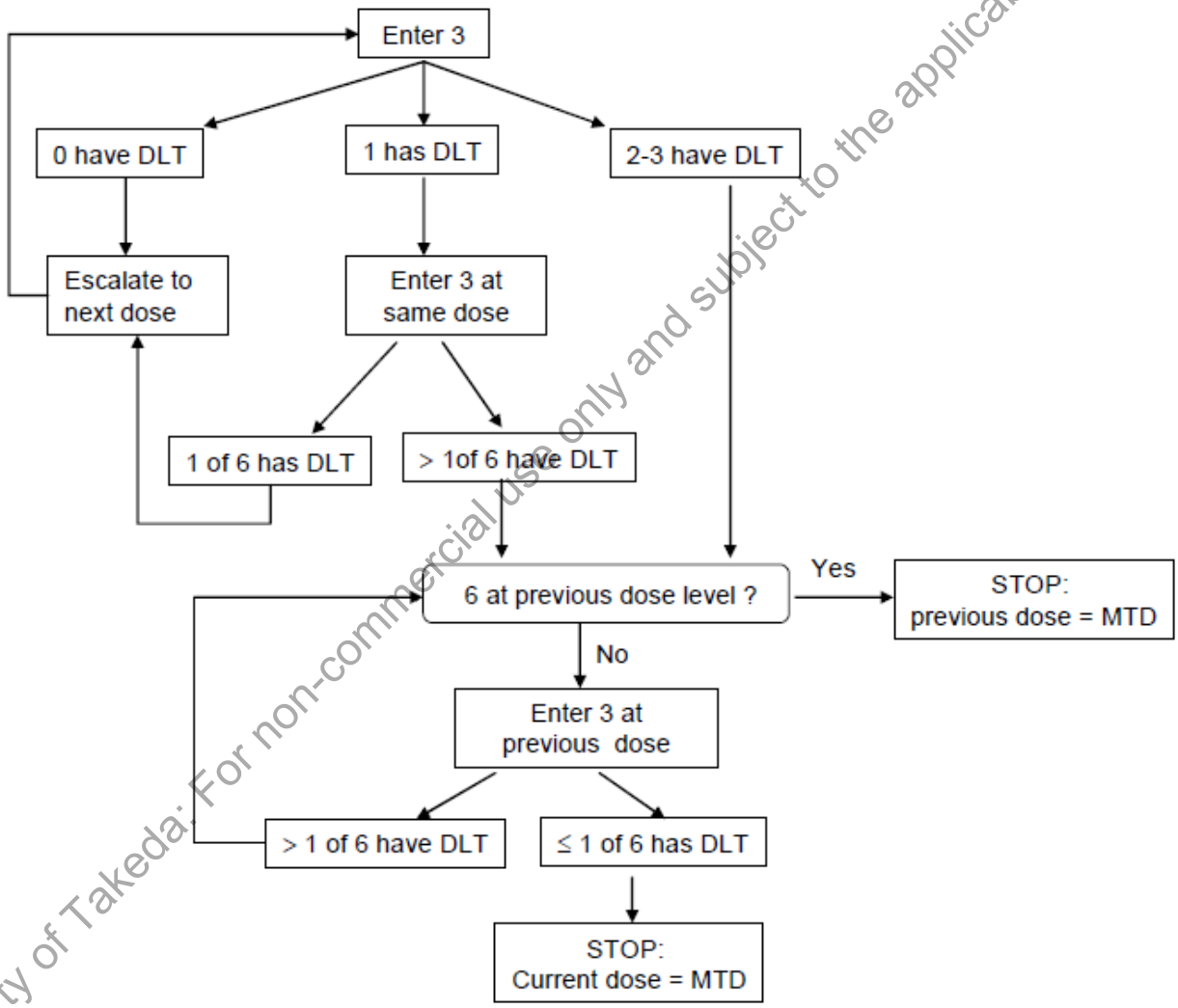
- If none of the patients in a cohort of 3 patients exhibits a DLT during the 28-day cycle, then the dose may be escalated for the next cohort of 3 patients.
- If 1 patient in a cohort of 3 patients exhibits a DLT, then that cohort will be expanded to a total of 6 patients.
- If ≤1 of 6 patients experiences a DLT, escalation will continue to the next higher dose level, at which 3 patients will be enrolled.
- If 2 or more patients (2 or more out of 3, or 2 or more out of 6) experience a DLT, dosing will de-escalate to the next lower dose level, at which 3 additional patients will be enrolled if 3

[redacted]

patients have been treated at that dose level. If 6 patients have been enrolled at the lower level with 1 or less DLT out of 6, dosing may stop and this dose level may be considered the MTD. The MTD is defined as the highest dose with a cohort of 6 patients having no more than 1 patient with a DLT.

Figure 8.a is a diagrammatical representation of the dose-escalation paradigm.

Figure 8.a Dose-Escalation Scheme



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

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or [redacted].

[redacted]

Before initiating the dosing of the next cohort, when safety data are available for all patients in the current cohort, key safety data will be reviewed and evaluated by the study team consisting of sponsor representatives and investigators who will review the safety of all treated patients and make decisions regarding dose escalation. In addition, changes to the dose-escalation scheme or dose schedule (dosing interval) may be considered. All decisions will be documented in writing. Any decision to modify the dose-escalation scheme (with the exception of testing intermediate dose levels) or dose schedule will be communicated to institutional review boards (IRBs), and the protocol will be amended accordingly.

8.4 TAK-079 Dose in Phase 1 Dose Confirmation Cohort

- TAK-079 will be given at a fixed dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD.
- In this cohort, safety and available efficacy, PK, [redacted] will be reviewed at least after 6 patients in each subgroup have received 1 cycle of therapy, then in an ongoing basis as per Takeda processes.

8.5 TAK-079 Dose in Phase 1 Combination Cohort

- TAK-079 will be given at a fixed dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD.
- PomDex are both standard of care agents and will be given in accordance with product labeling [Pomalyst USPI including Section 14.1; NCCN guidelines 2019].
- In this cohort, up to 6 patients will initially be enrolled. Safety in Cycle 1 will be reviewed in accordance with DLT definitions in Section 8.2.
- If 0 of 6 or 1 of 6 patients develop a DLT and additional 12 patients will be tested at the initial dose of TAK-079 [6 patients that are naïve to a prior anti-CD38 agent and 6 patients that have been exposed to a prior anti-CD38 agent], for an overall total of 18 patients.
- If 2 of 6 patients develop DLTs, an additional cohort of 6 patients will be tested at a de-escalated dose; an intermediate or more conservative dose schedule may also be implemented as a means to provide an overall lower dose. A lower dose of pomalidomide may also be considered based on the available safety data. If 0 of 6 or 1 of 6 patients develop TAK-079–related DLTs at the revised dose, an additional cohort of up to 12 patients (with eligibility as above regarding anti-CD38 naïve or exposed) will be tested at this dose level (in other words a dose lower than the initial dose, one that is intermediate or more conservative than the initial dose) or conservative dose schedule, for an overall total of 18 patients at the lower dose/conservative dose schedule. If 2 of 6 patients develop DLTs at the lower dose, this cohort will be stopped for further evaluation.

[redacted]

8.6 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for TAK-079 on the basis of the type and severity of AEs and causality determination by investigators (see Section 8.6.2). Further clarification can be obtained in consultation with the sponsor clinician (or designee).

8.6.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment for all cohorts use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- Absolute neutrophil count must be $\geq 1000/mm^3$.
- Platelet count must be $\geq 75{,}000/mm^3$.
- For therapy to resume, toxicity considered to be related to treatment with TAK-079 must have resolved to Grade ≤1 or baseline, or to a level considered acceptable by the physician. If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed for 1 week. At the end of that week, the patient should be re-evaluated to determine whether the criteria for re-treatment have been met. If there is a delay of a subsequent cycle longer than 28 days because of a drug-related AE, 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.
- For TAK-079 injections within the same cycle, the decision of holding treatment is left to the investigator's discretion based on clinical and analytical data, and also based on the toxicity that the patient experienced with previous injections in the same cycle. The investigator should differentiate between acute toxicity (like an IR) from which the patient has recovered at the time of the next injection, and subacute toxicity (for example, neutropenia) that might be worsened upon another injection if it is not on a clear recovery path. If the dose cannot be administered on the scheduled day, the patient can be reviewed at the investigator's discretion in the following 48 hours. If TAK-079 cannot be administered within a cycle in this 48-hour window, the dose will be missed and the patient scheduled for the next administration per the Schedule of Events (SOE; Appendix A).

8.6.2 Criteria for Dose Modification

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 TAK-079 may continue study treatment with the same dose, may have TAK-079 treatment held or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, 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 study drug 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 TAK-079.

Table 8.a provides general dose modification recommendations. When the dose of TAK-079 is withheld on the basis of these criteria, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed, until the toxicity resolves to Grade ≤1 or baseline. 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 monoclonal antibodies as a means to reduce dose intensity [5,26,27]. Patients experiencing a DLT (defined in Section 8.2) should be withdrawn from study treatment unless the sponsor approves subsequent treatment in a lower dose cohort.

See details for managing specific AEs in Section 8.11.

Table 8.a Dose Modification Recommendations for TAK-079 Toxicities

Criteria	Action
Grade 1 AEs	No dose interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same dose is 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. (Note Section 8.2 for AEs of short duration and/or that respond to medical management.) Note in phase 1, nonhematologic AEs Grade ≥3 may meet DLT criteria and as such patients should be withdrawn from further dosing unless the sponsor approves subsequent treatment in a lower dose cohort. Grade 3 or higher 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 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 TAK-079 administration does not commence within the prespecified window (Table 8.b) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date upon recovery as described above.

AE: adverse event; DLT: dose-limiting toxicity.

If initial dose interruption does not provide sufficient relief, permanent discontinuation of TAK-079 should be considered.

Table 8.b TAK-079–Related Toxicity Management

Dosing Frequency	Dose Missed	Dosing Resumption
Weekly (QW)	>3 days	Skip dose, move to next planned weekly dosing date
Biweekly (Q2W)	>7 days	Skip dose, move to next planned biweekly dosing date
Every 4 weeks (Q4W)	>21 days	Skip dose, move to next planned every 4 weeks dosing date

A TAK-079 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. Subjects missing ≥3 consecutive planned doses of TAK-079 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 TAK-079 during every-4-weeks dosing may be delayed (interrupted) up to 4 weeks. 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 TAK-079 that requires a dose delay (interruption) of more than 28 days should result in permanent discontinuation of TAK-079, unless both the investigator and the sponsor study clinician believe the patient is deriving clinical benefit.

8.6.3 Criteria for Discontinuing TAK-079 in Individual Patients (When Considering Dose Modification)

TAK-079 should be discontinued in patients experiencing an AE in Cycle 1 that meets the criteria for a DLT, unless the investigator considers re-treatment of the patient not to be dangerous and the sponsor approves subsequent treatment in a lower dose cohort. For Grade 4 (life-threatening) TEAEs, consider permanently withdrawing the patient from the study, except if the investigator determines that the patient is receiving clinical benefit, there are opportunities to provide supportive care to mitigate risk for the Grade 4 event to reoccur, and this approach (ie, the specific situation and mitigation plan) has been discussed with the sponsor. In these circumstances, treatment may be restarted when toxicity recovers to Grade ≤1 or baseline (see Table 8.a and Table 8.b).

8.7 Dose Modification Considerations for Patients in the Phase 1 Combination Cohort (TAK-079–PomDex Cohort) Only

- TAK-079 (study drug) will be given as noted in Section 8.5 through 8.6.3.
- Dexamethasone administered IV or orally at 40 mg/day on Days 1, 8, 15, 22, or 20 mg/day given on Days 1, 8, 15, and 22 for patients over 75 years of age (Pomalyst USPI, Section 14.1).
- Pomalidomide is a standard of care agents and will be given in accordance with product labeling (Pomalyst USPI).
- Treatment cycle will be 28-days as per product labeling until PD or unacceptable toxicity.

[redacted]

- PomDex will be procured by the site from commercial sources.

8.7.1 Dose Modification of Standard of Care Agents

- All toxicities that occur during the study will be actively managed following medical standard of care unless otherwise specified in the protocol.
- Toxicities should be attributed, whenever possible, to a specific drug (TAK-079 study drug, or standard chemotherapy agents pomalidomide or dexamethasone, as applicable) so that dose modifications can be made rationally. Reduction of 1 agent and not others is appropriate if toxicity is considered to be related primarily to one of the agents. If multiple toxicities are attributed to an individual agent (study drug or standard chemotherapy agent), dose adjustments should be made according to the guidelines for the most severe toxicity.
- Toxicities attributed to pomalidomide or dexamethasone, as applicable, should be managed according to the relevant guidelines in the respective product information [20,28].
- Once dose reduction has been implemented, unless otherwise stated specifically in the relevant product information and after discussion with the Sponsor Study Clinician (or designee), dose re-escalation should not occur.

8.8 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Chemotherapy and radiation therapy for the disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor's medical monitor and once PD is ruled out.
- Systemic corticosteroid use >10 mg/day (prednisone or equivalent).
- Live vaccines.
- Any investigational agent other than TAK-079, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.

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 received until 30 days after the final dose will be recorded in the electronic case report forms (eCRFs) (note additional information in Section 9.4.9 and Appendix A).
- The following medications and procedures are permitted while the patient is receiving the study drug:
  - For patients in the Combination Cohort (TAK-079–PomDex) only: patients must adhere to the pregnancy prevention program (Pomalyst REMS).

[redacted]

- For patients in the Combination Cohort (TAK-079–PomDex) only: patients receiving pomalidomide should be on routine thromboprophylaxis according to product label, published guidelines, and institutional practice [20,29].
- Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent).
- Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice. However, myeloid growth factors will not be allowed in Cycle 1 unless the study is in the expansion phase as their prophylactic use can interfere with DLT determination.
- Transfusions with RBCs and platelets as clinically indicated; however, platelet use will not be allowed in Cycle 1 unless the study is in the expansion phase because their prophylactic use can interfere with DLT determination.
- Localized radiation for pain management for osteolytic lesions.
- Concomitant treatment with bisphosphonates will be encouraged for all 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. If bisphosphonate therapy was not started before the study start, it should be initiated as soon as clinically indicated.
- Topical or inhaled steroids and short-acting β_2 adrenergic receptor agonists (eg, for the treatment of asthma) are permitted.
- Nonresorbable corticosteroids (eg, budesonide).
- Plasmapheresis.

8.10 Precautions and Restrictions

An interference with serological testing has been described with the anti-CD38 antibody daratumumab [23]. Daratumumab binds to CD38 on RBCs and results in a positive indirect antiglobulin test (Indirect Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not affected. It is possible TAK-079 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 TAK-079. 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.

Fluid deficits should be corrected before initiation of treatment and during treatment.

NSAIDs should be avoided with impaired renal function given the reported NSAID-induced renal failure in patients with decreased renal function.

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-079 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following:

- WOCBP must not be pregnant or lactating.
- 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 at least 90 days or 5 half-lives after the last dose of study drug (whichever is longer). Note the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [30,31], a conservative time frame to continue contraception would be 150 days. OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and 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 one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug. Note the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [30,31], a conservative timeframe to continue contraception would be 150 days. OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

[redacted]

For men and women patients enrolled in the Combination (TAK-079–PomDex) Cohort only: patients receiving pomalidomide must adhere to the Pomalyst REMS requirements per the product label [20].

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium, and uric acid levels must be performed. Patients with tumor lysis syndrome should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis as indicated).

8.11 Management of Specific Adverse Reactions

8.11.1 Handling of IRs

Patients should be carefully observed during TAK-079 injections. Trained trial staff at the clinic should be prepared to intervene in case of any systemic IRs and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators; also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of an IR (any grade), blood draws should be performed for central evaluation of [redacted], ADAs, [redacted]. These draws must not interfere with patient care and blood tests necessary for the acute care of the patient.

For additional details, refer to Section 9.4.15.3.

Grade 1 or 2 IR

In case of Grade 1 or 2 IRs (systemic signs or symptoms):

- Withhold therapy (also administration of remaining SC injections when full dose was not yet reached) until resolution to Grade 1 or maximum to Grade 2 as per the investigator's discretion.
    - If a patient experiences a Grade 1 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once the patient is stable per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.
    - If a patient experiences a Grade 2 IR mid-dosing, hold subsequent SC injections, evaluate the patient, treat symptoms, and once resolved to Grade 1 or resolved completely, per investigator's discretion, resume SC injections to achieve the full dose level. The remaining injections must be given 30 minutes apart, and the patient will be evaluated for IRs after each SC injection.
    - Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. Subsequent doses may have individual SC injections administered more frequently at the investigator's discretion with appropriate premedication and postmedication.

[redacted]

Grade 3 IR

In case of Grade 3 IRs (systemic signs or symptoms):

- Withhold therapy (also administration of remaining SC injections if full dose was not yet reached and therefore skip remaining injection[s]) until next scheduled TAK-079 SC administration, providing that the IR has recovered to Grade ≤1 at the time of the next scheduled TAK-079 dose. Patients who experience IRs must be treated according to the investigator's judgement and best clinical practice. At the time of the next dose after an IR, patients at a dose level requiring more than 1 SC injection should receive each injection 30 minutes apart. If no further IR, subsequent injections may be given more frequently at the investigator's discretion with appropriate premedication and postmedication.
- Permanently discontinue treatment after the third occurrence of Grade 3 IRs.

Grade 4 IRs

In case of Grade 4 IRs (systemic signs or symptoms):

Permanently discontinue treatment.

8.11.2 Injection Site Care

Prophylactic postinjection site care:

Apply 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).

8.11.3 Handling of Low Platelet Counts

Treatment decisions will be based on patient platelet counts assessed before any transfusion. Low platelet counts (Grade 4) should cause scheduled treatment to be postponed or to be permanently discontinued if recovery is delayed more than 14 days (see Table 8.a). If at any time the platelet count is less than 10×10^9/L, or if the patient shows a bleeding tendency considered to be due to thrombocytopenia occurring after initiation of TAK-079 treatment, the patient should be withdrawn from TAK-079 treatment. Platelet transfusion and daily monitoring of platelet counts, evaluation of coagulation parameters, and the Coombs test are recommended. These patients (that is, those who have platelets $<10\times10^9$/L if recovery is delayed more than 14 days OR with bleeding tendency due to thrombocytopenia OR with abnormal Coombs test) should be considered as having experienced an SAE.

For patients in the phase 1 Combination Cohort, thrombocytopenia is a known TEAE reported with pomalidomide and should be monitored and managed according to the product information [20].

[redacted]

8.11.4 Risk of Infection

The intended mechanism of action of TAK-079 may involve reduction of the subject's immune response. Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis treatment (eg, antiviral medication) may be initiated as clinically indicated, as determined by the investigator. Patients during the study should be followed closely for signs and symptoms of infection and treated as clinically indicated.

Until more clinical experience is gained with the use of TAK-079, it is prudent to avoid situations that may place subjects at increased risk of infection.

For patients in the phase 1 Combination Cohort, neutropenia is a known adverse drug reaction reported with pomalidomide and should be monitored and managed according to the product information [20].

8.11.5 Transfusion Risks

Blood samples from patients being treated with TAK-079 may show pan reactivity during pretransfusion testing. To facilitate the provision of blood components for such patients, it is recommended that a baseline phenotype or genotype be established before starting treatment with TAK-079. Patients should keep this information in case future transfusions are needed. If a patient requires RBC phenotyping after the start of TAK-079 treatment, dithiothreitol treatment of the patient's RBCs should be performed, in case of preexisting positivity to standard tests.

8.12 Blinding and Unblinding

This is an open-label study.

8.13 Description of Investigational Agents

[redacted]

8.14 Preparation, Reconstitution, and Dispensation

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

TAK-079 is an anticancer drug; as with other potentially toxic compounds, caution should be exercised when handling TAK-079.

8.15 Packaging and Labeling

Supplies of TAK-079 will be labeled according to the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

8.16 Storage, Handling, and Accountability

8.16.1 Storage and Handling

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label (see the Pharmacy Manual for additional information).

During shipping, vials will be protected from light and shipped as noted in the pharmacy manual. Each TAK-079 shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area should be maintained every day.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use of TAK-079.

The investigator is responsible for ensuring that deliveries of TAK-079 and other study materials from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Detailed dosage preparation instructions are provided in the Directions for Use section of the Pharmacy Manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the Pharmacy Manual.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each subject, and return to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the Pharmacy Manual.

8.16.2 Accountability and Destruction of Sponsor Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The investigator must maintain 100% accountability for all study medication (TAK-079) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

[redacted]

- Per standard clinical practice, a site representative, otherwise uninvolved with study conduct, will review the subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication. This review will be documented at the site.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Empty, partially used, and unused TAK-079 will be disposed of, retained, or returned to the sponsor or designee, as directed by the sponsor or designee.

The investigator must maintain a current inventory (Drug Accountability Log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and subjects' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the Pharmacy Manual.

8.17 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned using an 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 numbers (MED IDs) 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.

8.18 Standard Drug Procurement Procedures: Patients in the Combination Cohort Only

8.18.1 Pomalidomide

Pomalidomide will be procured by the site from commercial sources. Additional details are provided in the product information [20]. Patients receiving pomalidomide must adhere to the Pomalyst REMS program per the product label.

Pomalidomide capsules should be stored at temperatures in accordance with the instructions provided in the manufacturers product information.

8.18.2 Dexamethasone

Dexamethasone will be procured by the site from commercial sources. Additional details are provided in the product information (Decadron USPI).

Dexamethasone tablets should be stored according to the instructions provided in the manufacture's product information.

8.19 Other Protocol-Specified Materials

TAK-079 will be supplied for use in this clinical study. No other drugs (including PomDex in the Combination Cohort) or ancillary materials are supplied for use in this study.

[redacted]

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, any clinical laboratories centrally analyzing samples, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB/independent ethics committee (IEC). The screening period for this study is 21 days.

9.3 Treatment Group Assignments

All patients will receive open-label treatment with TAK-079 as indicated in respectively assigned treatment cohorts.

For phase 1 Combination Cohort (TAK-079–PomDex) Cohort only: patients must meet prespecified inclusion/exclusion criteria in Section 7.0 to be assigned to this cohort.

9.4 Study Procedures

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. This includes initial diagnosis date and MM staging at initial diagnosis using the International Staging System and Salmon-Durie Staging. Before dosing, the investigator should record the International Staging System as of study entry, which should be consistently used throughout the study.

Known cytogenetic alterations should also be collected. Prior treatment regimens, with each treatment duration (start and stop dates), the best response obtained with each therapy, and date/type of PD should be recorded. Refractoriness to previous treatments should be collected

following IMWG criteria (Appendix E). Confirm that the patient's current medical status does not include active chronic HBV, HCV, or HIV infection.

For patients who have received previous anti-CD38 therapy, the worst grade of infusion-related reactions should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

Information on any subsequent anticancer therapies will be collected during the PFS/OS follow-up periods.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured during the screening visit only. Weight will be measured on Day 1 of each treatment cycle, as indicated in Appendix A.

9.4.6 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and blood pressure. Vital sign measurements will be made before TAK-079 injection, and include supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position). All measurements should be performed in the same initial position, including heart rate and body temperature.

Blood pressure will also be measured before each injection, and at any time the patient complains of symptoms consistent with IR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

Vital signs will be measured at the visits specified in the SOE (Appendix A). 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 10.2.

9.4.7 Eligibility Criteria

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.

9.4.8 Pregnancy Test

WOCBP must have 2 negative pregnancy tests (human chorionic gonadotropin <5 mIU/mL) prior to starting study drug. A serum pregnancy test will be used during the screening period (within 10 to 14 days before the start of study drug). A serum pregnancy test must also be performed at baseline (within 24 hours before the start of study drug). A WOCPB is a sexually mature female

who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

During the study, if a menstrual period is delayed, absence of pregnancy in WOCBP must be confirmed by serum pregnancy test. Pregnancy tests may also be repeated during the study upon request by an IRB or if required by local regulations.

A urine pregnancy test is required in WOCBP at designated treatment visits (Appendix A) and also at the EOT visit.

Patients receiving pomalidomide in the Combination Cohort (TAK-079–PomDex) must adhere to the Pomalyst REMS program per the product label. Pregnancy tests may also be repeated during the study as per request of the IEC/IRBs or required by local regulations.

9.4.9 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had within 21 days before TAK-079 administration and up to 30 days after the last dose of TAK-079 (or the start of subsequent anticancer therapy, whichever occurs first) will be recorded on the eCRF. Trade name and international nonproprietary name/generic name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF. See Section 8.8 and Section 8.9 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.10 AEs

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the SOE. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of TEAEs and SAEs.

9.4.11 Enrollment

A patient is considered to be enrolled in the study at the first injection.

Procedures for completing the enrollment information are described in the Study Manual.

9.4.12 ECG

A single ECG will be collected at the screening visit for assessment of eligibility. A qualified person will interpret the ECG.

Time-matched triplicate 12-lead ECGs and PK samples will be collected in this study during Cycles 1 and 2 as specified in Appendix B. Although the number of scheduled ECG measurements will not be increased, the timing may be changed if emerging data indicate that an alteration in the ECG schedule is needed. Triplicate ECGs will be recorded electronically and transmitted to a central vendor for storage.

The triplicate ECG measurements should be completed before the PK blood draw. Collection of triplicate ECGs should be done according to institutional standards.

Single, 12-lead ECGs will be administered at all other designated visits (ie, after Cycle 2), as specified in Appendix A.

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) will be considered a TEAE, recorded on the source documentation and in the eCRF, and monitored as described in Section 10.2.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally (includes the direct and indirect Coombs tests). Exceptions are discussed below.

Handling of clinical laboratory samples will be outlined in the Study Manual. The [redacted], PK, and immunogenicity (ADA and potential neutralizing antibody [NAB]) assessments are to be performed centrally.

CD38 expression of MM cells will be assessed by multicolor flow cytometry; analysis will be done centrally. [redacted]

Decisions regarding eligibility for this study may be made using local laboratory determinations in the dose-escalation portion of phase 1 of this study. For dosing decisions, local hematology and chemistry laboratory results will be used.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters and urine sample parameters for analysis are shown in the tables below. Samples will be obtained as specified in the SOE (Appendix A). They will be performed locally only.

[redacted]

For Patients in Cohorts Receiving TAK-079 monotherapy:

Table 9.a Clinical Chemistry and Hematology Tests for Research Purposes

Hematology	Serum Chemistry	
ANC	Albumin	Creatinine clearance
Hematocrit	ALP	CRP
Hemoglobin	ALT	Glucose (nonfasting)
Platelet (count)	AST	GGT
Reticulocyte count	Bilirubin (total)	LDH
RBC count	BUN	Phosphate
WBC count with differential	Calcium	Potassium
Coagulation panel	Chloride	Sodium
	CO_2 (bicarbonate)	Total protein
	Creatinine	Urate (uric acid)

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: serine aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; GGT: γ-glutamyl transferase; LDH: lactate dehydrogenase; RBC: red blood cell; WBC: white blood cell.

Table 9.b Clinical Urinalysis Tests for Research Purposes

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

For estimation of creatinine clearance, the Cockcroft-Gault formula will be employed as follows:

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

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

[redacted]

For patients in the phase 1 Combination Cohort (TAK-079–PomDex) Cohort only:

Table 9.c Clinical Hematology and Chemistry: Standard of Care Laboratory Tests

Hematology	Chemistry	
Leukocytes with complete differential (total neutrophils [ANC], lymphocytes, monocytes, eosinophils, and monocytes)	Albumin	CO_2 (bicarbonate)
Platelet count	ALP	Creatinine
Hemoglobin	ALT	Estimated glomerular filtration rate
Serum pregnancy test	AST	Glucose
	B2- microglobulin	LDH
	Bilirubin (direct and indirect)	Potassium
	Calcium	Sodium
	Chloride	Urate

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: serine aminotransferase; LDH: lactate dehydrogenase.

Table 9.d Clinical Hematology and Chemistry: Tests for Research Purposes

Clinical Hematology or Chemistry	Serology antibody titers
Coagulation panel (PT, PTT, INR)	Hepatitis B
Indirect and direct coombs	Hepatitis C
C-reactive protein	HIV

INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time.

Table 9.e Clinical Urinalysis: Tests for Research Purposes

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity, appearance, and color
Nitrite	Urobilinogen
Occult blood	Microscopic assessment (a)

(a) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. All procedures and tests should be done as outlined in the SOE (Appendix A). After 24 months on treatment, the patient may be monitored according to standard clinical practice per the treating physician.

9.4.13.2 Prestudy Prognostic Risk Assessment

A blood sample will be collected for serum β_2 microglobulin at screening to assess patient disease status. Results will be analyzed locally.

[redacted]

9.4.14 Disease Response Assessments

Patients will be assessed for disease response according to the IMWG criteria ([21,22]; Appendix E). In addition, in patients that have myeloma measurable by serum free light chains, MR will be defined as a reduction of ≥25 but ≤49% in the difference between involved and uninvolved FLC levels.

For patients in the phase 1 Combination Cohort (TAK-079–PomDex) Cohort only:

Table 9.f Myeloma Disease Assessments: Tests Standard of Care Tests

Serum/Urine	Bone Marrow/Imaging
SPEP	Bone marrow biopsy and/or aspirate [(a)]
UPEP	Cytogenetics [presence of del (17), t(4:14), and t(14:16) at a minimum]
Immunofixation (serum and urine)	Imaging (skeletal survey, CT scan, PET/CT scan, MRI)
Quantification immunoglobulin levels	
Serum FLC	

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.
(a) The BMAs only at Cycle 2D1, C4D1, C7D1, and C13D1 are for research purposes unless these align with a suspected CR then this procedure would be Standard of Care.

For all patients:

After 24 cycles on treatment, the patient may be monitored according to standard clinical practice per the treating physician.

Serum and urine response assessments will be performed no later than the first day of every treatment cycle, before the patient receives treatment with TAK-079. Patients with myeloma measurable by SPEP only will have 24-hour urine collected at screening and EOT and to document PR, very good partial response (VGPR), CR, or PD.

Imaging tests will be done per Appendix A and as described in Section 9.4.14.1. The same imaging technique should be used throughout the study to facilitate consistent disease assessment.

Responses should be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum FLCs as outlined in Appendix A. One BMA assessment has to occur to document CR; no second bone marrow confirmation is needed.

Note that to determine a response of sCR, BMA immunohistochemistry or immunofluorescence for kappa:lambda ratio, as well as serum FLC assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

PD may be confirmed per standard clinical practice at the site. Local laboratory results may be used to confirm PD.

Blood samples, 24-hour urine sample, BMA, and imaging done for disease response assessment will be done locally.

9.4.14.1 Computed Tomography/Magnetic Resonance Imaging

Scans will be performed at a minimum at screening and at the EOT visit. All treatment phase and follow-up scans should use the same imaging modality used at screening.

For patients with documented extramedullary disease, a whole-body x-ray, positron emission tomography-computed tomography (PET-CT) scan, computed tomography (CT) scan (includes low-dose CT), or magnetic resonance imaging (MRI) scan will be performed as outlined in Appendix A. The screening scan may be performed up to 21 days before first dose of TAK-079; however, if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, that image can be used as baseline and does not need to be repeated as part of screening. If disease is documented, then a repeat PET-CT scan, CT scan, or MRI scan should be performed as required to document response or PD.

Additional surveys (x-ray, CT, or MRI) may also be performed at the investigator's discretion, eg, in case of bone pain. Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.4.14.2 Quantification of Immunoglobulins

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained at the screening visit, predose on Day 1 of every cycle, and at all visits per Appendix A. Analysis of Ig will be performed locally.

9.4.14.3 Quantification of M-Protein

A predose blood and 24-hour urine sample will be obtained at the screening visit, Day 1 of every cycle, and at all visits per Appendix A.

The samples will be tested locally. M-protein in serum and urine will be quantified by SPEP and UPEP.

9.4.14.4 Serum FLC Assay

Serum samples will be obtained predose on Day 1 of every cycle and at all visits, per Appendix A, for the serum FLC assay (including quantification of kappa and lambda chains and ratio). Blood samples will be analyzed locally.

9.4.14.5 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at the screening visit, predose on Day 1 of every cycle, to confirm CR, and at all response assessment visits as per Appendix A. Immunofixation testing will be performed in a local laboratory.

[redacted]

9.4.14.6 BMAs

Central Laboratory Evaluations

BMAs will be taken during the screening period and at the beginning of designated study visits at Cycles 2, 4, 7, and at Cycle 13, with some aspirate samples sent for central analysis (note Table 9.g).

Local Laboratory Evaluations

Disease Assessment

A BMA will be obtained at screening for disease assessment (if a standard BMA was drawn within 5 weeks before consent, that BMA can be used as baseline and does not need to be repeated as part of screening unless cytogenetic evaluation is not available). A BMA will also be obtained at any time to assess CR or as needed to investigate suspected PD. Requirements for BMA assessments to confirm disease responses are defined above and will be analyzed locally (see Section 9.4.14).

Cytogenetics

Patients who do not have historically documented cytogenetic results for the high-risk abnormalities of del (17), t(4:14), and t(14:16) will have cytogenetic evaluation performed on the BMA sample at screening. Cytogenetic evaluation may be performed using fluorescence in situ hybridization or conventional cytogenetics (karyotype). At a minimum, cytogenetic markers must include the 3 high-risk abnormalities of del(17), t(4:14), and t(14:16). Additional abnormalities (ampl 1q, del13, or del1p) may also be tested. Cytogenetics will be analyzed locally, according to local standards.

9.4.15 [redacted], PK, [redacted], and Immunogenicity Samples

9.4.15.1 Primary Specimen Collection for PK, [redacted], and [redacted] Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix B for the measurement of serum concentrations of TAK-079 and in Appendix A for [redacted].

The primary specimen collection is presented in Table 9.g. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Table 9.g Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for TAK-079 PK	Serum	PK measurements	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
[redacted]	[redacted]	[redacted]	Mandatory
Serum sample for immunogenicity	Serum	Immunogenicity assessments	Mandatory
Serum sample for direct and indirect Coombs test	Serum	Immunogenicity assessments	Mandatory

PK: pharmacokinetics.

9.4.15.2 PK Measurements

Serum samples for the measurement of concentrations of TAK-079 will be collected at multiple time points as specified in Appendix B.

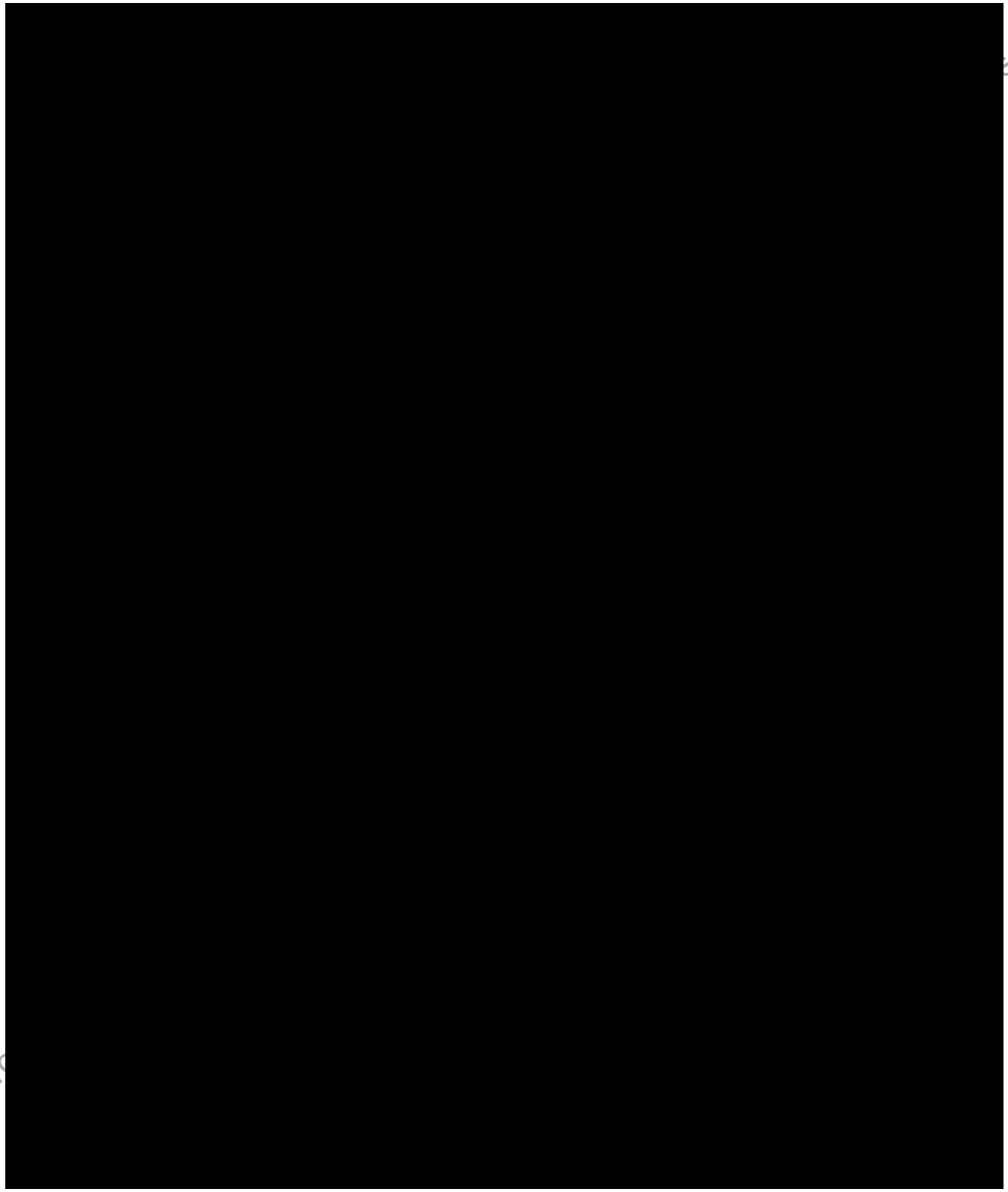
The timing, but not the total number, of samples may be modified during the study on the basis of emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual.

9.4.15.3 [redacted]

[redacted]

[redacted]



[redacted]

9.4.15.4 Immunogenicity Assessments

ADA Assessment

Serum samples for the assessment of anti–TAK-079 immunogenicity will be collected at the study visits specified in Appendix A. A blood sample will be collected before administration of TAK-079 (ie, prior to dosing on Day 1; baseline value), then subsequently before TAK-079 dosing at each designated visit (postbaseline values), and at visits for any patient who experiences a TEAE considered by the investigator to be consistent with hypersensitivity/IR.

A sample will initially be screened for ADA titer. If a sample is detected as ADA positive, it may be assessed for neutralizing activity.

Direct and Indirect Coombs Testing

Serum samples for direct and indirect Coombs testing will be collected at time points specified in Appendix A. These tests will be performed locally.

9.5 Completion of Study Treatment (for Individual Patients)

Patients will be considered as having completed study treatment if they discontinued study drug for any reason as outlined below in Section 9.7.

9.6 Completion of Study (for Individual Patients)

Patients will receive TAK-079 until they experience PD, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor (see additional details in Section 9.8).

Patients will have a follow-up visit 30 days after the last dose of study drug or prior to the start of subsequent alternative anticancer therapy, to permit the detection of any delayed AEs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, the start of subsequent anticancer therapy, study termination, or until 12 months after discontinuation of study treatment, whichever occurs first.

[redacted]

Patients will be followed every 12 weeks for OS until death, loss to follow-up, consent withdrawal, or study termination.

It is anticipated that the duration of the study will be approximately 42 months (3.5 years).

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Patient experiences an AE or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.
- Withdrawal by patient.
- Female patient has confirmed pregnancy.

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

- AE/SAE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.
- Other.

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

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

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 by patient (mandatory immediate discontinuation of study agent).
- Death.
- PD.

- Other.

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

9.9 Study Compliance

Study drug will be administered 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 stop treatment for any reason other than progressive disease will continue to have progression-free follow-up visits (additional details in Section 9.6). Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 4 weeks from EOT until the occurrence of PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first.

Patients who stop treatment due to PD will continue to have OS visits. Patients will be followed every 12 weeks for OS after documented PD until death, loss to follow-up, consent withdrawal, or study termination.

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.

See the SOE (Appendix A) for appropriate assessments during follow-up.

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

[redacted]

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 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 4.03, effective date 14 June 2010 [25]. 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 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 <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 and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

Cognizant
United States and Canada
Toll-free fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

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

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

pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [25]. 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 next-line subsequent anticancer therapy, or 6 months after PD has occurred, whichever comes first.

SAEs:

- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 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 caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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

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

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

Product	Call Center	Phone Number	E-mail	Fax
TAK-079	DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE Form should be completed and sent to Cognizant (refer to Section 10.2)

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

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

[redacted]

11.0 STUDY-SPECIFIC COMMITTEES

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

[redacted]

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, pretreatment events, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of

a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

[redacted]

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of any study drug.

DLT-evaluable analysis set: The DLT-evaluable analysis set will include patients who receive all Cycle 1 doses of TAK-079 and have completed Cycle 1 procedures, or experience a DLT in Cycle 1 in the phase 1 portion of the study. The DLT-evaluable population will be used to determine the RP2D/MTD.

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of any study drug.

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, and DOR.

[redacted]

PK analysis set: The PK analysis set will include those patients from the safety analysis set who have sufficient dosing data and TAK-079 concentration-time data to permit the calculation of PK parameters.

Immunogenicity analysis set: The immunogenicity analysis set will include those patients from the safety population who have baseline and at least one postbaseline sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings, will be summarized using descriptive statistics. 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 if necessary.

[redacted]

13.1.3 Efficacy Analysis

Data from any efficacy assessments performed after the specified follow-up time will not be collected on the eCRF; if such data are collected, these data will not be analyzed.

The preliminary efficacy of TAK-079 for MM will be evaluated by measuring the ORR (defined as the proportion of patients who achieved a PR or better during study) and the composition of sCR, CR, VGPR, and PR as defined by the IMWG Uniform Response Criteria (see Appendix E). In addition, MR will be analyzed (see Section 9.4.14 and Appendix E).

In addition, the efficacy of TAK-079 will be assessed in patients by measuring DOR, PFS, and 1-year OS. TTR will also be measured.

13.1.4 PK Analysis

PK parameters will be estimated using noncompartmental analysis methods. Parameters will be calculated for individual patients included in the PK analysis set using the TAK-079 concentration-time data. The calculated PK parameters will include, but not be limited to, C_{max}, t_{max}, and AUC_{last} (as permitted by the data).

PK parameters will be summarized using descriptive statistics. Individual TAK-079 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 PK data collected in this study may also contribute to future population PK analyses of TAK-079. These population PK analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Similarly, the time-matched PK and triplicate ECG data collected in this study may contribute to future concentration-QT interval corrected for heart rate (QTc) analyses. These analyses may include data collected in other TAK-079 clinical studies. The analysis plan for the concentration-QTc analysis will be separately defined, and the results will be reported separately.

13.1.5 [redacted]

[redacted]

13.1.6 Immunogenicity Analyses

TAK-079 immunogenicity will be analyzed using the immunogenicity analysis set. The proportion of patients with positive ADA (transient and persistent) will be summarized, and the proportion of patients in phase 2a with positive neutralizing ADA during the study may be

[redacted]

summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined. NABs may also be assessed in patients.

The immunogenicity of TAK-079 will be assessed by determining anti–TAK-079 antibody incidence and characteristics (eg, titer, transiently, and persistently ADA; and possible neutralizing activity). Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment. Summaries will be provided separately for each study phase and by dose, as applicable. The incidence of immunogenicity will be calculated. The impact of anti–TAK-079 antibodies on the PK profile, drug efficacy, and clinical safety will be evaluated, if possible.

13.1.7 Safety Analysis

The safety and tolerability of TAK-079 will be assessed by the recording and analysis of TEAEs (NCI CTCAE version 4.03; [25]), vital signs, physical examination, serum chemistry and hematology, urinalysis, ECG, and concomitant medications.

TEAEs will be summarized using the safety analysis set and will be coded using the MedDRA. Data will be summarized using PT and primary SOC.

In the phase 2a portion of this study, Grade 4 or higher nonhematological toxicity will be monitored starting from the first 10 enrolled patients and then every 10 patients. If the stopping bounds of ≥4/10 and ≥6/20 have been reached, accrual to the study will be suspended to allow for investigation. After consideration by the study team, a decision will be made as to whether accrual can be resumed. The bounds 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 18% with a prior beta distribution with parameters 0.4 and 1.6 for the binomially distributed toxicity rate [32].

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

It is expected that approximately 100 patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately 48 patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with RRMM.

A 3+3 dose escalation schema will be used for dose escalation as described in Section 8.3.2.

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile.

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and [redacted] before the phase 2a of this study is opened to enrollment. In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose and schedule: 12 patients with RRMM that is anti-CD38 naive and up to 6 patients with RRMM that is refractory to an anti-CD38 therapy. In the Combination Cohort, approximately 18 patients with

[redacted]

RRMM that has been previously treated with at least 2 prior therapies and that is refractory to the last therapy will be enrolled.

In phase 2a, up to a total of 48 patients will be treated to provide a preliminary estimate of the ORR in 2 expansion cohorts of patients with RRMM: up to 24 patients with RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 13.a shows the width of the 80% CI, based on the observed ORR in a cohort size of 24 patients, for a range of observed response rates.

Table 13.a 80% Confidence Interval Based on the Observed ORR

[redacted]

N = 24 patients.
ORR: overall response rate.

[redacted]

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix C. 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 federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

[redacted]

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

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

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

[redacted]

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

15.3 Patient Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

[redacted]

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 in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's 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 to find 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 callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

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

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, 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 patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Informed consent (b)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
HBV, HCV, and HIV	X								
Height and weight (c)	X	X				X			
ECOG performance status	X	X				X			
ECG (d)	X	X				X			
		ECG measurements additionally on **Days 2, 3**, and **4** for Cycles 1 and 2 (see Section 9.4.12).							
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).								
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).								
Dosing for Phase 1 Dose Escalation Cohort									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 injection (f)		X	X	X	X	X	X	X	X
Dosing Patients in Dose Confirmation Cohort									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 SC injection (f)		X	X	X	X	X	X	X	X

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Dosing Patients in Combination Cohort Only									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 SC injection (f)		X	X	X	X	X	X	X	X
Pomalidomide		Day 1-21 in each cycle							
Dexamethasone		Day 1, 8, 15, and 22 in each cycle							
Laboratory assessments									
Serum chemistry (g)	X	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X				X			
Pregnancy test (j) (k)	X	X				X			
Response assessments for MM									
Investigator disease assessment (t)						X			
Serum M-protein	X	X				X			
Urine M-protein (l)	X	X				X			
Serum FLC assay (m)	X	X				X			
Immunofixation - serum and urine (n)	X	X				X			
Quantification of Ig	X	X				X			
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)	X								
Biological assessments									
Bone marrow aspiration (BMA) (p)	X					X			
Serum sample for TAK-079 PK (q)		X	X	X	X	X	X	X	X
		PK sampling additionally on **Days 2, 3**, and **4** for Cycles 1 and 2.							

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
[redacted]									
Serum sample for immunogenicity (ADA/titer) (s)		X		X		X			
Serum sample for direct and indirect Coombs test	X	X				X			

Footnotes appear on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 3 Through 6

Study Period (Phases 1 and 2a)	Treatment Phase (Every 2 Weeks)							
	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Height and weight (c)	X		X		X		X	
ECOG performance status	X		X		X		X	
ECG (d)	X		X		X		X	
Physical examination	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).							
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).							
Dosing Patients in Dose Escalation Cohort								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 injection (f)	X	X	X	X	X	X	X	X
Dosing Patients in Dose Confirmation Cohort								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 SC injection (f)	X	X	X	X	X	X	X	X
Dosing Patients in Combination Cohort Only								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 SC injection (f)	X	X	X	X	X	X	X	X
Pomalidomide	Day 1-21 in each cycle							
Dexamethasone	Day 1, 8, 15, and 22 in each cycle							
Laboratory assessments								
Serum chemistry (g)	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X

[redacted]

Treatment Period Continued: Cycles 3 Through 6

Study Period (Phases 1 and 2a)	Treatment Phase (Every 2 Weeks)							
	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Urinalysis (i)	X		X		X		X	
Pregnancy test (j) (k)	X		X		X		X	
Response assessments for MM								
Investigator disease assessment (t)	X		X		X		X	
Serum M-protein	X		X		X		X	
Urine M-protein (l)	X		X		X		X	
Serum FLC assay (m)	X		X		X		X	
Immunofixation - serum and urine (n)	X		X		X		X	
Quantification of Ig	X		X		X		X	
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)							X	
Biological assessments								
Bone marrow aspiration (BMA) (p)			X					
Serum sample for TAK-079 PK (q)	X	X	X	X	X	X	X	X
[redacted]								
Serum sample for immunogenicity (ADA/titer) (s)	X		X		X		X	
Serum sample for direct and indirect Coombs test	X		X		X		X	

Footnotes appear on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	C7D1	C8D1, CXD1	Up to 30 days After Last Dose	--------	--------
Window Allowed	±2 days	±2 days	±7 days	± 7 days	± 7 days
Laboratory assessments					
Height and weight (c)	X	X	X		
ECOG performance status	X	X	X		
ECG (d)	X	X	X		
Physical examination	X	X	X		
Vital signs (e)	X	X	X		
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK 079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3). SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3)				
Dosing Patients in Dose Escalation Cohort					
Pre-injection medication	X	X			
TAK-079 injection (f)	X	X			
Dosing Patients in Dose Confirmation Cohort					
Pre-injection medication	X	X			
TAK-079 SC injection (f)	X	X			
Dosing Patients in Combination Cohort Only					
Pre-injection medication	X	X			
TAK-079 SC injection (f)	X	X			
Pomalidomide	Day 1-21 each cycle				
Dexamethasone	Day 1, 8, 15, and 22 each cycle				

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	C7D1	C8D1, CXD1	Up to 30 days After Last Dose	--------	--------
Window Allowed	±2 days	±2 days	±7 days	± 7 days	± 7 days
Laboratory assessments					
Serum chemistry (g)	X	X	X		
Hematology (h)	X	X	X		
Urinalysis (i)	X	X	X		
Pregnancy test (j) (k)	X	X	X		
Response assessments for MM					
Investigator disease assessment (t)	X	X	X	X	
Serum M-protein	X	X	X	X	
Urine M-protein (l)	X	X	X	X	
Serum FLC assay (m)	X	X	X	X	
Immunofixation - serum and urine (n)	X	X	X		
Quantification of Ig	X	X	X		
Skeletal survey: WB X-ray, CT, low dose CT, PET-CT, or MRI scan (o)			X		
Biological assessments					
Bone marrow aspiration (BMA) (p)	X	X (Cycle 13 only)			
Serum sample for TAK-079 PK (q)	X	X	X		
[redacted]					
Serum sample for immunogenicity (ADA/titer) (s)	X	X	X		
Serum sample for direct and indirect Coombs test	X	X	X		

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
Study Period (Phases 1 and 2a)	**Cycle 7**	**Cycle 8 and beyond**	**EOT/Early Termination**	**PFS Follow-Up Every 4 Weeks**	**OS Follow-Up Every 12 Weeks**
Cycle Day	**C7D1**	**C8D1, CXD1**	**Up to 30 days After Last Dose**	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Subsequent anticancer therapy				X	X
Survival (u)					X

Footnotes begin on the next page.

[redacted]

ADA: antidrug antibody; AE: adverse event; BMA: bone marrow aspirate; [redacted]; C: cycle; CR: complete response; CT: computed tomography; CXD1: Day 1 of additional treatment cycles (ie, after Cycle 8); D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: Informed Consent Form; Ig: immunoglobulin; IMWG: International Myeloma Working Group; IR: injection reaction; MM: multiple myeloma; MRI: magnetic resonance imaging; OS: overall survival; PD: disease progression; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetics; PR: partial response; RBC: red blood cell; SAE: serious adverse event; SOE: Schedule of Events; [redacted]; VGPR: very good partial response; WB: whole body; WBC: white blood cell.

(a) The screening period is 21 days (ie, Days -21 to Day -1).
(b) Written informed consent must be obtained before performing any protocol-specific procedure.
(c) Height will be measured only at the screening visit. Weight will be measured at indicated visits.
(d) A single ECG will be collected at the screening visit. PK time-matched triplicate 12-lead ECGs will be collected during Cycles 1 and 2, as specified in Appendix B. Single 12-lead ECGs will be administered for all other designated visits (ie, after Cycle 2).
(e) Vital signs are measured prior to TAK-079 injection. Blood pressure will also be measured before starting each 2 mL injection, and at any time the patient complains of symptoms consistent with IR. Vital signs include temperature, pulse, respiratory rate, and blood pressure.
(f) Time and anatomical site should be recorded for each injection (see Figure 6.a and Section 8.0).
(g) Serum β_2 microglobulin levels will be measured at screening only. Refer to Section 9.4.13.1 for a list of clinical chemistry laboratory assessments.
(h) Refer to Section 9.4.13.1 for a list of hematology laboratory assessments.
(i) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. Refer to Section 9.4.13.1 for a list of urinalysis assessments.
(j) Pregnancy test (Refer to Section 9.4.8): Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A serum pregnancy test will be performed during screening (within 10-14 days before start of study drug). A serum pregnancy test is required within 24 hours before start of study drug.
(k) Pregnancy test (refer to Section 9.4.8): On-treatment: a urine pregnancy test is required at designated study visits. A urine pregnancy test is required at the follow-up visit in women of childbearing potential. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.
(l) Sampling required only if urine M-protein is measurable at Day 1 (visit 2). Per IMWG, required in all patients for PR, VGPR, CR, at EOT, and to determine PD during PFS follow-up.
(m) Blood sample obtained for the serum FLC assay to include quantification of kappa and lambda chains and ratio). To be analyzed locally.
(n) Will also be collected to confirm a CR.
(o) May be performed up to 21 days before first dose of TAK-079. Additional surveys (x-ray, CT, or MRI) may be performed at the investigator's discretion, eg, in case of bone pain. If disease is documented, then a repeat scan should be performed as required to document a response or PD.
(p) BMAs: [redacted] At screening, a standard BMA drawn prior to consent is acceptable provided this is collected within 5 weeks before the first dose; cytogenetics will be done locally (See Section 9.4.14.6).
For response assessment purposes, when a CR is suspected based on laboratory values, a BMA is required to confirm a CR. At the time of this procedure (at CR), 1 aspirate sample is analyzed locally for evaluation of disease, [redacted]
(q) Blood samples for PK characterization will be collected at time points specified in Appendix B PK Sampling Schedule.
[redacted]

[redacted]

(s) Serum samples for immunogenicity assessment will be collected at baseline (before TAK-079 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.
(t) Patients who discontinue treatment for reasons other than PD will continue to be followed every 4 weeks until PD, death, start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first.
(u) Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

[redacted]

Appendix B PK Sampling Schedule

PK Assessments: Cycle 1

	Cycle 1										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG: electrocardiogram; PK: pharmacokinetic(s); SC: subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

PK Assessments: Cycle 2

	Cycle 2										
	Day 1 (a)		Day 2		Day 3		Day 4		Day 8 (a)	Day 15 (a)	Day 22 (a)
	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	Triplicate ECG (b)	PK	PK	PK	PK
Predose (within 1 hour before first SC injection)	X	X							X	X	X
5 minutes after FINAL SC injection (±2 min)		X (c)									
4 hours after first SC injection (±30 min)		X									
6 hours after first SC injection (±30 min)	X	X									
8 hours after first SC injection (±1 hour)	X	X									
24 hours after first SC injection (±2 hours)			X	X							
48 hours after first SC injection (±2 hours)					X	X					
72 hours after first SC injection (±2 hours)							X	X			

ECG: electrocardiogram; PK: pharmacokinetic(s); SC: subcutaneous.
When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.
(b) Collection of triplicate ECGs should begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window.
(c) If multiple SC injections are required to administer the intended dose, this PK sample should be collected after administration of the final injection. All other assessments should be performed in reference to the first injection.

[redacted]

PK Assessments: Cycle 3 to Cycle 10

	Cycle 3 to Cycle 6		**Cycle 7 to Cycle 10**
	Day 1 (a)	**Day 15 (a)**	**Day 1 (a)**
Predose (within 1 hour before first SC injection)	X	X	X

PK: pharmacokinetic; SC: subcutaneous.
(a) The timing of the morning visits should occur at approximately the same time as the morning SC administration times on previous days of the cycle.

[redacted]

Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

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

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

[redacted]

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

[redacted]

Appendix E IMWG Criteria

IMWG Definition of MM [21,22,33]

- Clonal bone marrow plasma cells ≥10%* or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically.
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of the normal range or >2.75 mmol/L (>11 mg/dL).
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL).
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L.
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡.
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%.
  - Involved: uninvolved serum free light chain ratio§ (FLC) ≥100.
  - >1 focal lesions on MRI studies.

* Clonality should be established by showing κ/λ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
† Measured or estimated by validated equations.
‡ If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
§ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, United Kingdom). The involved FLC must be ≥100 mg/L. Each focal lesion must be 5 mm or greater in size [33].

[redacted]

IMWG Uniform Criteria for Response [21,22,33]

Category of Response	Response Criteria
sCR	Criteria for CR as defined below, with the addition of a normal FLC ratio, and an absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed (a).
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; 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; 2 consecutive assessments are needed (b).
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 >4 colors).
Molecular CR	CR as defined, plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; 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; 2 consecutive assessments are needed (c).
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed (a) no known evidence of progressive or new bone lesions if radiographic studies were performed.
Minimal response (MR) (b)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the 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). In this study, in patients that have myeloma measurable by serum free light chains, MR will be defined as a reduction of ≥25 but ≤49% in the difference between involved and uninvolved FLC levels.
SD (c)	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

Source: Rajkumar SV et al, 2011 and Palumbo A et al, 2014 [21,22]
CR: complete response; FLC: free light chain; IMWG: International Myeloma Working Group; MR minimal response; ORR: overall response rate; PR: partial response; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.
(a) Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
(b) For relapse-refractory myeloma only.
(c) These categories do not contribute to the ORR.

Before the institution of any new therapy, sCR, CR, and VGPR 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.

PD is defined as an increase of ≥25% from lowest response value in any of the following:

a) Serum M-protein (absolute increase must be ≥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

b) Urine M-protein (absolute increase must be ≥200 mg/24 hour), and/or

c) Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL).

d) Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%).

OR

a) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

b) Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Clarifications to IMWG criteria for coding PD: 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 tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

[redacted]

Appendix F ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al,1982 [24]

[redacted]

Appendix G Detailed Description of Amendments to Text

All changes made in the protocol, other than typographical and formatting changes, are listed below in the order they appear in the protocol. Changes are listed by sections, only the sections with modifications are listed and only the paragraphs containing changes within the section are represented. All changes made in the body of the protocol are also reflected in the Study Summary. Changes to the Study Summary are not listed here.

Note: All deletions have been identified by ~~strikethrough~~.

All revisions have been identified as **bold red text**.

All moved text has been identified as underlined green text and the previous location is identified as ~~green strikethrough~~

REVISED PROTOCOL SECTIONS

3.1 List of Abbreviations

Abbreviation	Term
AML	**acute myeloid leukemia**
POEMS ~~syndrome~~	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes **syndrome**
PomDex	**pomalidomide in combination with dexamethasone**
PT	**Preferred Term**
REMS	**Risk Evaluation and Mitigation Strategy**
SOC	**System Organ Class**
SOE	~~Schedule~~**schedule** of ~~Events~~**events**

4.0 INTRODUCTION

4.2.2 Preliminary Findings From the Dose Escalation Period of This Study

As of 05 March 2018, 19 patients have been enrolled through the first 4 dose planned cohorts (45, 135, 300, and 600 mg). In this ongoing study, the most common (in >2 patients) treatment-emergent AEs by Medical Dictionary for Regulatory Activities (**MedDRA**) **Preferred Term (PT) regardless of causality in the total population as of 05 March 2018 are anaemia (n = 5 patients, insomnia, headache, and hypertension (n = 4 patients each), and upper respiratory tract infection, fatigue, and decreased appetite (n = 3 patients each). All AEs have been Grade 1 or 2; 2 events were reported as drug-related Grade 3 AEs (decreased neutrophil count and anemia [in 1 patient each] both of which were transient. No patient experienced dose-limiting toxicities (DLTs), injection site reactions, discontinued TAK-079 due to TEAEs, or died on-study; 2 patients experienced SAEs, none were reported as treatment related (1 event was pretreatment). No patient has been demonstrated to have had CRS symptoms; 1 patient in the 135 mg cohort did report transient facial flushing Cycle 2 Day 1, which the investigator reported as drug related.**

In the original phase 1 dose Escalation Cohorts, TAK-079 was given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD. Based on a review of available clinical activity, PK, and pharmacodynamic findings, the dose of TAK-079 as monotherapy in the Confirmation Cohort and when added to PomDex in the Combination Cohort will be 300 mg in the same schedule as follows:

Confirmation Cohort: TAK-079 will be given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD in subsequent cycles.

Combination Cohort: TAK-079 will be given weekly for 8 weeks during Cycles 1 and 2 (8 doses), every other week during Cycles 3 to 6 (8 doses), and then once every 4 weeks until PD in subsequent cycles with PomDex given according to product information (Pomalyst USPI, including Section 14.1).

4.3 Known and Potential Benefits and Risks to Patients ~~with~~With TAK-079

…..

TAK-079 has now been administered to patients with advanced RRMM (TAK-079-1501; this study). Only mild or moderate (Grade 1 or 2) TEAEs were observed as described above.

…..

4.3.1 Potential Risks

Based on the mechanism of action of TAK-079, potential AEs may include infusion or injection site reactions, **CRS,** hematological effects, and infections.

4.3.1.1 Infusion and Injection Site Reactions

….

In this study (TAK-079-1501) in patients with RRMM at doses up to 600 mg (given with 3 SC injections), no injection site reactions have been reported.

…..

4.3.1.2 Cytokine Release Syndrome

…..

In the FIH study conducted in healthy human subjects, rarely-observed symptoms consistent with mild CRS were reported particularly at higher doses, and they did not require dose adjustment or interruption. **In this study (TAK-079-1501) in patients with RRMM at doses up to 600 mg, 1 transient event on Cycle 2 Day 1 of drug-related flushing in a single patient in the 135 mg cohort could conservatively be a symptom of a systemic infusion reaction; however, no other symptoms have been reported in this or other patients.**

….

4.3.1.3 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered doses of TAK-079 higher than the NOAEL of 0.3 mg/kg**. The NOAEL was based on occurrence of thrombocytopenia in 1 of 14 monkeys and is believed to be species specific. In the TAK-079 FIH (TAK-079_101) and RRMM (this study TAK-079-1501) at doses up to 600 mg, no decrease in platelet counts below the lower limit of normal related to TAK-079 were seen (note 1 event of grade 3 thrombocytopenia was reported as related to progression of the underlying advanced myeloma in study TAK-079-1501)**.

…

4.3.1.4 Infections

…

In the TAK-079 FIH study, mild infections, specifically nasopharyngitis was reported. In the study in patients with RRMM (TAK-079-1501, this study), 4 of 19 patients treated at doses up to 600 mg reported an AE in the infection and infestation MedDRA System Organ Class (SOC); the most common AE reported was upper respiratory infection (n = 3); all were grade 2 and only 1 was reported as related to study drug.

…

4.3.2 Overall Benefit and Risk Assessment for This Study

…

The emerging preliminary safety profile, as detailed above and in the current Investigator Brochure, indicate that TAK-079 is generally well tolerated with manageable and reversible AEs. The potential toxicities can be managed by clinical monitoring and standard medical interventions. It is possible that TAK-079 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-079, patients will be carefully monitored closely for signs and symptoms of systemic and injection site reactions with appropriate management of these events. Guidance for the management of AEs are provided in Section 8.11. Depending on the severity of the reaction, drug dosage can be reduced by dose modification (holding or delaying) of the scheduled treatment within a cycle as provided in Section 8.6, and may include discontinuation of TAK-079.

In patients with advanced RRMM, TAK-079 has shown early signs of antitumor activity as evidenced by at least 50% reduction in disease burden in some patients and prolonged disease stabilization in others. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of TAK-079.

[redacted]

4.4.1 Rationale for the Starting Dose of TAK-079

…..

The dose used in the Confirmation Cohort and the Combination Cohorts is the expected RP2D from the dose Escalation Cohorts, based on preliminary PK and PD results from the dose Escalation Cohort.

Relevant to the Combination Cohort, lenalidomide is established therapy in NDMM [17,18] therefore patients for whom lenalidomide is no longer a treatment option, because of previous exposure, intolerance, or are refractory to lenalidomide, represent a clinically relevant population with unmet need. Nonclinical studies demonstrate that pomalidomide inhibits proliferation of lenalidomide-resistant cells [19]. Clinically, PomDex, an all oral regimen, is approved for patients who have previously received lenalidomide [20]. Adding an anti-CD38 monoclonal antibody to it, especially one that is given SC, could be beneficial and convenient to patients as compared with IV administered anti-CD38 monoclonal antibodies. PomDex will be given at the dose and schedule recommended in the product information (Pomalyst USPI including Section 14.1) while TAK-079 will be given at the RP2D in the revised schedule described in Section 6.1.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

Phase 1

The primary objective of the phase 1 portion of the study is to determine the safety and tolerability of TAK-079 monotherapy **and when combined with a backbone regimen of PomDex** in patients with RRMM.

…

5.1.2 Secondary Objectives

Phase 1

The ~~Phase~~**phase** 1 secondary objectives are:

- To investigate a potential MTD/RP2D of TAK-~~079.~~**079 as a single agent and when added to a backbone regimen of PomDex.**
- To evaluate the immunogenicity of TAK-~~079.~~**079 as a single agent and when added to a backbone regimen of PomDex.**
- To characterize the PK of TAK-~~079.~~**079 as a single agent and when added to a backbone regimen of PomDex.**
- To provide a preliminary evaluation of the clinical activity of TAK-~~079.~~**079 as a single agent and when added to a backbone regimen of PomDex.**

[redacted]

…..

5.2.3 Phase 1 Secondary Endpoints

The secondary endpoints for phase 1 are:

- RP2D based on both safety and efficacy outcomes **as a single agent and when added to a backbone regimen of PomDex**.
- Summary statistics for the following PK parameters **as a single agent and when added to a backbone regimen of PomDex**:

  Maximum observed concentration (C_{max}).

  Time of first occurrence of C_{max} (t_{max}).

  Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- Preliminary evaluation of antitumor activity of TAK-~~079~~079**, as single agent and in combination with PomDex,** will be assessed for patients with MM by measuring:

  ORR, defined as the proportion of patients who achieved a PR (50% tumor reduction) or better during the study as defined by the IMWG Uniform Response Criteria ([~~17,18~~**21,22**]; Appendix E).

  Proportion of patients who achieved a minimal response (MR), defined as 25% tumor reduction ~~([17,18~~**, including in patients with disease measurable by serum free light chains (FLCs) ([21,22**]; Appendix E).
- Anti–TAK-079 antibody incidence and characteristics.

5.2.4 Phase 2a Secondary Endpoints

The secondary endpoints for phase 2a are:

- DLT-like frequencies and other TEAEs occurring over the course of extended treatment with TAK-079, including information about dose modification, treatment discontinuation, and vital signs.
- Summary statistics for the following PK parameters: C_{max}, t_{max}, and AUC_{last}.
- Anti–TAK-079 antibody incidence and characteristics.
- Proportion of patients who achieved MR, defined as 25% tumor reduction.
- Duration of response (DOR), defined as the time from the date of the first documentation of response to the date of the first documented PD.
- **Progression-free survival (**PFS**)**, defined as the time from the date of the first dose until the earliest date of PD, defined by IMWG criteria, or the date of death due to any cause ([~~17,18~~**21,22**]; Appendix E).

- **Overall survival (**OS**)**, defined as the time from the date of first dose to the date of death due to any cause.
- Time to response (TTR), defined as the time from the date of the first dose to the date of the first documentation of response (PR or better).

6.0 STUDY DESIGN

6.1 Overview of Study Design

...

The phase 1 portion of the study will evaluate administration of **single agent** TAK-079 for DLT(s) to determine the MTD/RP2D for further assessment in phase 2a. A recommended dose below the MTD may be identified based on safety, clinical, PK, [redacted] data. The safety and tolerability of TAK-079 will be assessed by recording and analyzing TEAEs from medical review of vital signs, physical examinations, serum chemistry and hematology analyses, urinalyses, ECGs, review of concomitant medications, dose modifications, and treatment discontinuations.

MM is a heterogenous disease requiring treatments across multiple lines of therapy despite recent advances. The pace of MM treatment has been rapid in recent years and even with a shift towards triplet regimens from doublet regimens, patients are still relapsing from, ineligible for, or intolerant to such combinations. Further the treatment paradigm is fragmented due to patient factors as well as disease factors and acceptance of recently approved regimens is gaining but remains variable. Therefore, this study will continue to evaluate patients with relapsed or refractory disease, including those who have not progressed following daratumumab, in an effort to more fully understand the activity of TAK-079 in patients who represent the highly heterogeneous population seen in current clinical practice. Before enrolling into the phase 2a phase of the study, additional patients will be enrolled in a dose Confirmatory Cohort to better understand the safety and clinical activity of the TAK-079 RP2D based on preliminary PK/[redacted] data.

More patients now receive combinations of lenalidomide, bortezomib, dexamethasone with or without daratumumab as first-line treatment, yet their disease still progresses. Most develop lenalidomide-resistant disease; thus, alternatives to lenalidomide are required in later lines of therapy. Pomalidomide with dexamethasone is approved for patients following therapy with lenalidomide and a proteasome inhibitor; however, the duration of response is short (7.4 months) [20]. Evidence is emerging that adding an IV administered anti-CD38 agent to PomDex can help prolong response duration [23]. TAK-079, a SC administered anti-CD38 monoclonal antibody, is showing early signs of antimyeloma activity as a monotherapy in patients with advanced RRMM. Adding TAK-079 to the PomDex backbone could provide benefit to patients both in terms of improved antimyeloma activity over each agent alone, and would be more convenient to patients as compared with administration of IV administered anti-CD38 agents (ie, a TAK-079, a SC agent, added to the all oral PomDex regimen). Hence a new cohort will open to evaluate this combination. Information about the dose, safety, and activity of TAK-079 added to a standard backbone regimen of PomDex in

[redacted]

patients with RRMM who have received at least 2 prior therapies and have demonstrated PD on or within 60 days of the completion of the last therapy will be collected.

The preliminary efficacy of TAK-~~079~~079, **as monotherapy and when added to PomDex,** will be evaluated by measuring the ORR, defined as the proportion of patients who achieved a PR or better during study, as defined by IMWG (Appendix E; [~~17,18~~21,22]). In addition, the efficacy of TAK-079 will be assessed by measuring MR, PFS, DOR, and OS; TTR will also be measured.

Once enrolled into the ~~study~~**phase 1 Dose Escalation phase**, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered as once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD. Patients will receive ongoing treatment with TAK-079 until they experience PD, unacceptable toxicities, or ~~withdrawal~~**withdraw** due to other reasons (see Section 6.3).

In the phase 1 Confirmation Cohort Phase, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD.

- **In this cohort, up to 6 patients that are refractory to an anti-CD38 agent will be enrolled.**
- **Further in this cohort, approximately 12 patients that have RRMM disease (per prior therapy inclusion criteria Section 7.0) and are naïve to an anti-CD38 agent will be enrolled.**

In the Combination Cohort, patients will receive TAK-079 via SC administration in each 28-day cycle of treatment, administered at a dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and then once every 4 weeks thereafter until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1).

- **In this cohort, up to 6 patients will initially be enrolled. Safety in Cycle 1 will be reviewed in accordance with DLT definitions in Section 8.2.**
- **If 0 of 6 or 1 of 6 patients develop a DLT an additional 12 patients will be tested at the initial dose of TAK-079 [6 patients that are naïve to a prior anti-CD38 agent and 6 patients that have been exposed to a prior anti-CD38 agent], for an overall total of 18 patients.**
- **If 2 of 6 patients develop DLTs all available data will be reviewed before making decisions about study conduct (See details in Section 8.5).**

The Confirmation Cohort and the Combination Cohort may start in parallel and will run independently.

~~Phase 1~~**All cohorts** will consist of the following phases/periods: screening, treatment, and follow-up:

- Screening period (visit 1): Days -21 to Day -1.
- Treatment period (visit 2/ongoing): ~~Once~~

[redacted]

- **Original dose Escalation Cohort: once**-weekly treatment for 8 doses (Cycles 1 and 2), starting on Day 1, followed by treatment once every 2 weeks for 8 doses (Cycles 3-6), followed by treatment once every 4 weeks thereafter (Cycle 7 and beyond), continuing until patients experience PD, unacceptable toxicities, or withdrawal due to other reasons.

- **Dose Confirmation Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD.**

- **Combination Cohort: once weekly for 8 weeks in Cycles 1 and 2 (8 doses), once every 2 weeks for 16 weeks (8 doses) in Cycles 3 to 6, and once every 4 weeks thereafter (Cycles 7 and beyond) until PD. PomDex will be administered according to the product labeling (Pomalyst UPSI, including Section 14.1 describing dexamethasone dosing).**

    - Follow-up period (**end of treatment [**EOT**]** visit): Patients who discontinue study treatment will be followed for approximately 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to monitor safety/AEs. Patients who discontinue treatment for reasons other than PD will continue to be followed for PFS every 4 weeks from the EOT visit until PD, death, the start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first. Patients who discontinue for PD will be followed for OS after the EOT visit. All patients will be followed for OS every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

In phase 1, approximately 6 doses will be evaluated in ascending cohorts of 3- **to** 6 patients per cohort. Cohorts may be expanded by enrolling additional patients to further inform selection of the RP2D. Dose selection for phase 2a will take place after review of the available safety, efficacy, PK, [redacted] data obtained from the phase 1 portion of the study.

In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose (300 mg); 12 patients will have been previously treated (see Section 7.0), up to 6 patients will have been previously treated and are refractory to an anti-CD38 therapy (see Section 7.0). In the Combination Cohort, approximately 18 patients will be enrolled who have received prior therapy and have demonstrated PD on or within 60 days of completion of the last therapy, note Section 7.0.

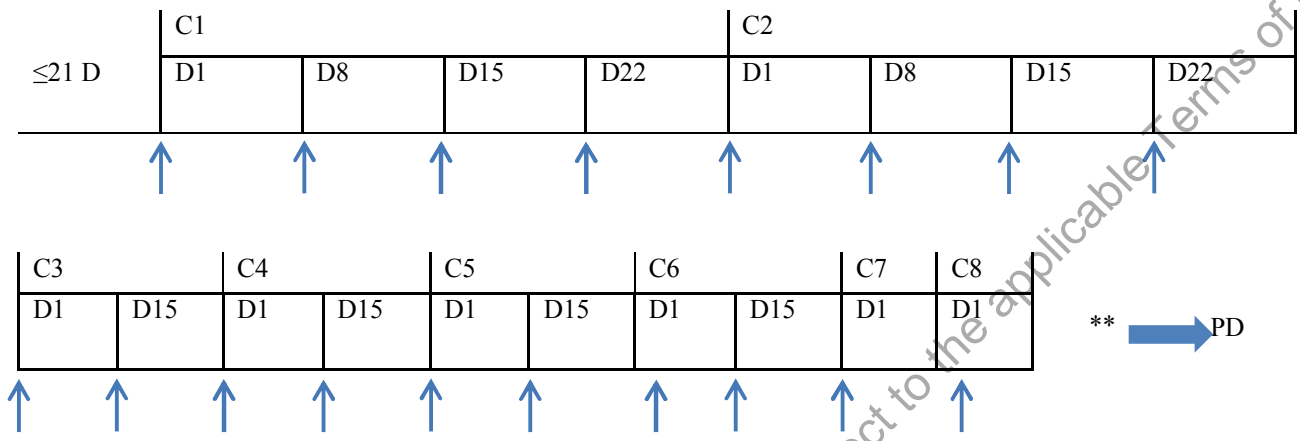
It is expected that approximately ~~42~~**100** patients will be enrolled in total for **the** phase 1 **cohorts** and **phase** 2a combined.

Study procedures and assessments, with their time points, are shown in Appendix A. The study schematic diagram is shown in Figure 6.a.

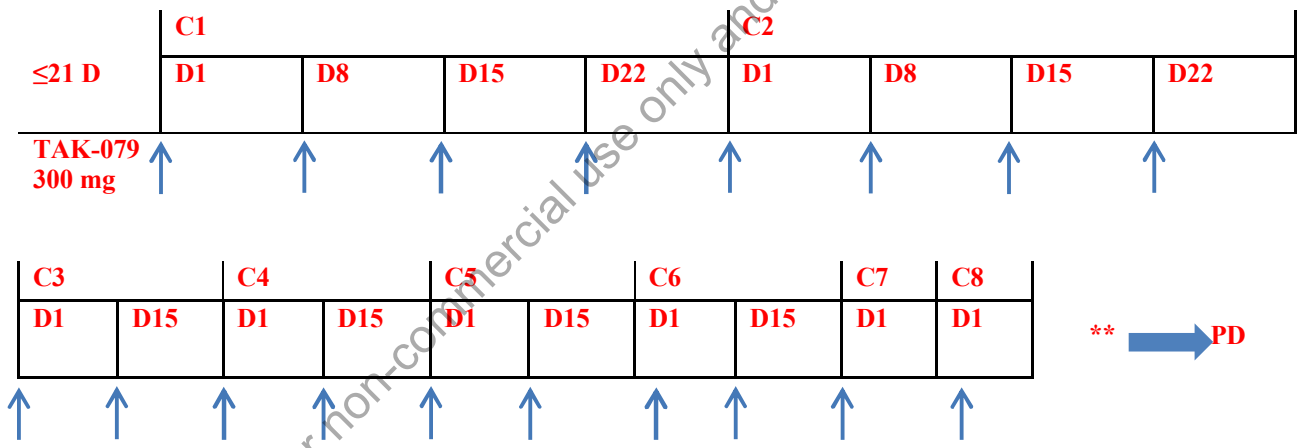
[redacted]

Figure 6.a Overall Study Schematic Diagram

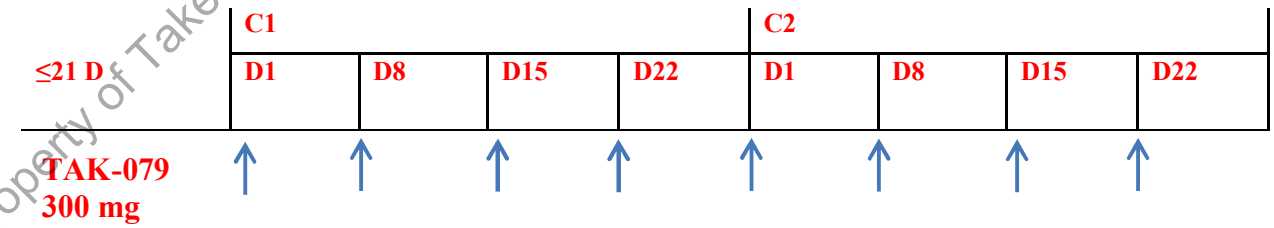
Treatment Cycle: original phase 1 dose Escalation Cohort



Treatment Cycle: phase 1 dose Confirmation Cohort

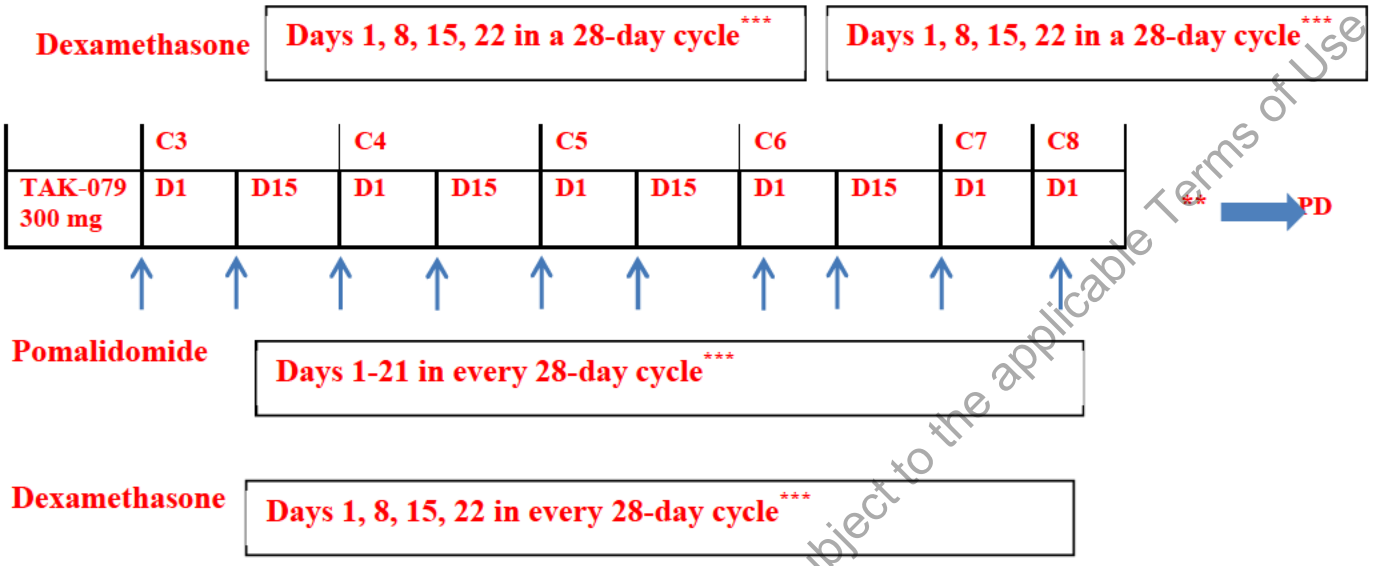


Treatment Cycle: new Combination Cohort



Pomalidomide | **Days 1-21 in a 28-day cycle*****

[redacted]



C=: Cycle; D=: Day; PD=: progressive disease; R2PD=: recommended phase 2 dose; SC=: subcutaneous.
Dose Escalation: 45, 135, 300, 600, 1200, and 1800 mg.
Cohorts in phase 1 may be expanded to further inform selection of the RP2D.
The RP2D determined in phase 1 will be further assessed in approximately ~~18~~48 patients in phase 2a.
* For dose levels where multiple SC injections are needed to administer the full prescribed dose, the Cycle 1 Day 1 dose SC injections will be given with a 30 minute interval in between each SC injection. Thereafter, if there are not clinically significant IRs, the SC injections may be given together without the waiting period.

** → = dosing every 28 days until disease progression.
↑ = TAK-079 dose.

*****Dose Confirmation and Combination cohort the dose of TAK-079 is 300 mg. In the Combination cohort the dose of pomalidomide and dexamethasone is per product labeling.**

6.2 Number of Patients

For phase 1, approximately ~~24~~55 patients are planned to be enrolled, including the expansion of additional patients in selected cohorts to further inform selection of the RP2D. For phase 2a, approximately ~~18~~48 patients are planned.

In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose and schedule: 12 patients with RRMM that is anti-CD38 naive and up to 6 patients with RRMM that is refractory to an anti-CD38 therapy. In the Combination Cohort, approximately 18 patients with RRMM that has been previously treated with at least 2 prior therapies and that is refractory to the last therapy will be enrolled.

In phase 2a, approximately 48 additional patients will be treated to provide a preliminary estimate of the ORR in 2 expansion cohorts of patients with RRMM: up to 24 patients with RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an anti-CD38 therapy phase 2a of the study will also provide a more robust estimate of the safety profile at the MTD/RP2D.

Details on the definition of evaluable patients and sample size are given in Section 13.1.

[redacted]

The study is planned to be conducted in the United States in approximately ~~4~~**7** investigational centers ~~for phase 1 and in a total of 6 investigational centers for phase 2a.~~**, although the sponsor may add more centers depending on enrollment rates.**

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive TAK-079 until they experience PD as defined by IMWG criteria [~~17,18~~**21,22**] (Appendix E), unacceptable toxicity, or any other discontinuation criterion is met (see Section ~~8.4.3~~**8.6.3** and Section 9.7). **In the combination cohort, additionally patients will receive PomDex until they experience PD as defined by IMWG criteria.** The maximum duration of treatment is expected to be 12 months **for patients receiving monotherapy and approximately 18 months for patients in the combination cohort**; however, patients with clinical benefit (per investigator and as agreed by the sponsor's study clinician) can continue on treatment ~~beyond 1 year~~ with the explicit approval of the sponsor's study clinician **(see Section 6.3.5 for Posttrial Access)**.

Patients will be evaluated 30±7 days after the last dose of TAK-079 (follow-up visit) or before initiating subsequent systemic anticancer therapy, for detection of any delayed TEAEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final analyses for the clinical study report ~~will~~**may** be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with ~~TAK-079 plus the EOT visit~~**single agent TAK-079, 18 months of combination therapy,** or after the ~~EOT visit of the~~ last patient ~~entering~~**completes** the ~~study~~**EOT visit** if the sponsor terminates the study ~~early~~**earlier** (Table 6.a).

6.3.4 Total Study Duration

The final analyses for the clinical study report may be conducted after all patients enrolled in the study have had the opportunity to complete 12 months of treatment with ~~TAK-079~~**single agent TAK-079, 18 months of combination therapy,** or after the last patient completes the EOT visit if the sponsor terminates the study earlier.

It is anticipated that this study will last for approximately ~~36~~

42 months (~~3~~**3.5** years).

6.3.5 Posttrial Access

At the conclusion or termination of the study or termination of a treatment arm in the study, if patients are, in the opinion of the investigator and confirmed by the sponsor, experiencing a clinically important benefit, TAK-079 treatment may be continued in this study or another extension or rollover study, if and when such a study is made available, upon request by the investigator and agreement by the sponsor. Continued access to TAK-079 for participants will be terminated for those individuals who no longer benefit from TAK-079, the benefit-risk no longer favors the individual, if TAK-079 becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy

becomes available. Posttrial access may be terminated in areas where marketing authorization has been rejected, the development of TAK-079 has been suspended or stopped by the sponsor, or TAK-079 can no longer be supplied. Only for patients enrolled into the Combination Cohort, the backbone agents ongoing at this time will continue to be procured by the site from commercial sources.

7.0 STUDY POPULATION

Phase 1 dose Confirmation Cohort: Adult patients with relapsed and/or refractory multiple myeloma who have been previously treated with at least a PI, an IMiD, and a steroid. Patients should have refractory disease or be intolerant to at least 1 PI and at least 1 IMiD, and they should have either received 3 or more prior therapies or received at least 2 prior therapies if one of those therapies included a combination of a PI and an IMiD. Patients who have had a previous autologous stem cell transplant will have additionally been exposed to an alkylating agent; however, patients who have not had a previous autologous stem cell transplant may not have been exposed to an alkylating agent per standard practice. Up to 6 patients will be refractory to an anti-CD38 agent and approximately 12 patients in this cohort should be anti-CD38 naïve.

Combination Cohort: Adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated PD on or within 60 days of the completion of the last therapy. The first 6 patients enrolled may be either naïve to a prior anti-CD38 antibody or may have been exposed to one previously (if exposed note washout period in Table 7.a). Once safety data have been reviewed, the following patients enrolled at the RP2D/MTD will be: naïve to a prior anti-CD38 monoclonal antibody (approximately 6 patients) or exposed to a prior anti-CD38 monoclonal antibody (approximately 6 patients; note washout period in Table 7.a).

7.1 Inclusion Criteria

…

5. Female patients who:

- Are WOCBP must not be pregnant or lactating.
- 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 at least 90 days or 5 half-lives after the last dose of study drug, whichever time period is longest **(See Section 8.10)**, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not

acceptable methods of contraception. Female and male condoms should not be used together.)

- **Patients enrolling in the Combination Cohort (TAK-079–PomDex) only must adhere to the Pomalyst REMS requirements per the product label.**

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

   - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug **(See Section 8.10)**, OR

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

   - **Patients enrolling in the Combination Cohort (TAK-079–PomDex) only must adhere to the Pomalyst REMS requirements per the product label.**

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

8. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and must be willing to return to the investigational center for the follow-up procedures and assessments specified in this protocol.

9. ~~Requires additional therapy, as determined by the investigator.~~**Patients in the Combination Cohort (TAK-079–PomDex) only must be able to take concurrent prophylactic anticoagulation per standard clinical practice as directed by the investigator and the Pomalyst product information.**

10. Documentation of RRMM as defined by the IMWG criteria (Appendix E; [~~17,18~~**21,22**]).

11. For patients with MM, 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.

[redacted]

12. Prior therapy, patients should meet all the following criteria:

Patients in the dose Escalation Cohort (escalation phase) and patients in the dose Confirmation Cohort;

- Patient should be previously treated with at least a PI, an IMiD, **and a steroid. Note: Patients who have had a previous autologous stem cell transplant will have additionally been exposed to** an alkylating agent~~, and a steroid.~~**; however, patient who have not had a previous autologous stem cell transplant may not have been exposed to an alkylating agent per standard practice.**
- Patient should be refractory or intolerant to at least 1 PI and at least 1 IMiD.
- Patient should either have received ≥3 prior lines of therapy or should have received at least 2 prior lines of therapy if one of those lines included a combination of PI and IMiD.
- In phase 1, previous exposure to an anti-CD38 agent, as a single agent or in combination, is allowed but is not required. **[Patients in the dose Escalation Cohort]**
- **In phase 1 dose Confirmation Cohort, 2 subgroups will be enrolled: up to 6 patients will be enrolled that meet above prior therapy criteria and are refractory at any time to at least 1 anti-CD38 agent and approximately 12 patients will be enrolled that meet above prior therapy criteria but are anti-CD 38 naïve.**

Patients in the Combination Cohort (TAK-079 added to PomDex cohort only):

- **Patients have undergone prior therapy with ≥2 prior anti-myeloma therapies (line of therapy defined below).**
- **Patient has either relapsed or relapsed and refractory disease. Should have progressed on or within 60 days of completing the last anti-myeloma therapy (refractory defined below).**

13. In the phase 2a portion of the study, **up to 2 cohorts of** patients with ~~MM must also have been~~**RRMM may be enrolled: 1 that is** refractory to at least 1 anti-CD38 mAb therapy at any time during treatment~~.~~ **and 1 that is naïve to daratumumab. Available safety and efficacy data will be used to make decisions about the patient cohorts to be enrolled in the phase 2a portion. The final decision on the phase 2a cohorts will be made by sponsor representatives following review of all available data considering stopping rule thresholds. (see Section 13.1.7)**

..

7.2 Exclusion Criteria

19. POEMS (~~Polyneuropathy~~**polyneuropathy**, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, monoclonal gammopathy of unknown significance, smoldering myeloma, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, or IgM myeloma.

[redacted]

20. ….

21. For patients in the Combination Cohort (TAK-079–PomDex) only: patient has previously received pomalidomide or has hypersensitivity to thalidomide or lenalidomide.

8.0 STUDY DRUG

8.1 Study Drug Administration

…

8.1.1 Predose and Postdose Medication

Premedications are required in phase 1 and phase 2a.

The clinical site is responsible for sourcing any premedications outlined in the protocol**.**

*8.1.1.1 Predose Medication****: Phase 1 Dose Escalation and Dose Confirmation Cohorts***

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration 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.
- Antipyretics: oral acetaminophen (650 to 1000 mg).
- Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).
- Montelukast 10 mg (or equivalent leukotriene inhibitor).

NOTE: For any patients with a history of COPD, consider prescribing postinfusion medications, such as short- and long-acting bronchodilators, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional inhaled postinfusion medications may be discontinued.

~~Premedications are required in phase 1 and phase 2a.~~

~~The clinical site is responsible for sourcing any premedications outlined in the protocol~~

8.1.1.2 ***Predose Medications: Phase 1 Combination Cohort (TAK-079–PomDex) Only***

Before each injection, patients will receive the following premedications 1 to 3 hours prior to the start of TAK-079 administration on each dosing day:

- **Antipyretics: oral acetaminophen (650 to 1000 mg).**
- **Antihistamine: oral or IV diphenhydramine (25 to 50 mg, or equivalent).**
- **Montelukast 10 mg (or equivalent leukotriene inhibitor).**

NOTE: For any patients with a history of COPD, consider prescribing postinfusion medications, such as short- and long-acting bronchodilators, and inhaled corticosteroids. After the first 4 infusions, if the patient experiences no major IRs, these additional inhaled postinfusion medications may be discontinued.

[redacted]

8.1.1.3 Postdose Medications ***(All Patients)***

...

8.4 TAK-079 Dose in Phase 1 Dose Confirmation Cohort

- **TAK-079 will be given at a fixed dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD.**
- **In this cohort, safety and available efficacy, PK, [redacted] will be reviewed at least after 6 patients in each subgroup have received 1 cycle of therapy, then in an ongoing basis as per Takeda processes.**

8.5 TAK-079 Dose in Phase 1 Combination Cohort

- **TAK-079 will be given at a fixed dose of 300 mg once weekly for 8 weeks (8 doses), once every 2 weeks for 16 weeks (8 doses), and once every 4 weeks thereafter until PD.**
- **PomDex are both standard of care agents and will be given in accordance with product labeling [Pomalyst USPI including Section 14.1; NCCN guidelines 2019].**
- **In this cohort, up to 6 patients will initially be enrolled. Safety in Cycle 1 will be reviewed in accordance with DLT definitions in Section 8.2.**
- **If 0 of 6 or 1 of 6 patients develop a DLT and additional 12 patients will be tested at the initial dose of TAK-079 [6 patients that are naïve to a prior anti-CD38 agent and 6 patients that have been exposed to a prior anti-CD38 agent], for an overall total of 18 patients.**
- **If 2 of 6 patients develop DLTs, an additional cohort of 6 patients will be tested at a de-escalated dose; an intermediate or more conservative dose schedule may also be implemented as a means to provide an overall lower dose. A lower dose of pomalidomide may also be considered based on the available safety data. If 0 of 6 or 1 of 6 patients develop TAK-079–related DLTs at the revised dose, an additional cohort of up to 12 patients (with eligibility as above regarding anti-CD38 naïve or exposed) will be tested at this dose level (in other words a dose lower than the initial dose, one that is intermediate or more conservative than the initial dose) or conservative dose schedule, for an overall total of 18 patients at the lower dose/conservative dose schedule. If 2 of 6 patients develop DLTs at the lower dose, this cohort will be stopped for further evaluation.**

8.6 ~~8.4~~ Dose Modification Guidelines

...

8.6.1 ~~8.4.1~~ Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment ~~with TAK-079 will~~**for all cohorts** use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

[redacted]

...

8.6.2 ~~8.4.2~~ Criteria for Dose Modification

....

Table 8.a Dose Modification Recommendations for TAK-079 Toxicities

Criteria	Action
Grade 1 AEs	No dose interruptions.
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue it at the same dose is 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. (Note Section 8.2 for AEs of short duration and/or that respond to medical management.) Note in phase 1, nonhematologic AEs Grade ≥3 may meet DLT criteria and as such patients should be withdrawn from further dosing unless the sponsor approves subsequent treatment in a lower dose cohort. Grade 3 or higher thrombocytopenia with bleeding should result in a dose interruption until the AE resolves to Grade ≤1 or baseline, then resume at the same dose. ~~Medical considerations should eliminate Coombs positivity before restarting (note Table 8.b).~~
Grade 4 (life-threatening) AEs	Patients with Grade 4 AEs 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. ~~Medical consideration should eliminate Coombs positivity before restarting (note Section 8.4.3 and Table 8.b).~~
AEs of all grades	If TAK-079 administration does not commence within the prespecified window (Table 8.b) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date upon recovery as described above.

AE=**:** adverse event; DLT=**:** dose-limiting toxicity.

8.7 Dose Modification Considerations for Patients in the Phase 1 Combination Cohort (TAK-079–PomDex Cohort) Only

- **TAK-079 (study drug) will be given as noted in Section 8.5 through 8.6.3.**
- **Dexamethasone administered IV or orally at 40 mg/day on Days 1, 8, 15, 22, or 20 mg/day given on Days 1, 8, 15, and 22 for patients over 75 years of age (Pomalyst USPI, Section 14.1).**

[redacted]

- **Pomalidomide is a standard of care agents and will be given in accordance with product labeling (Pomalyst USPI).**
- **Treatment cycle will be 28-days as per product labeling until PD or unacceptable toxicity.**
- **PomDex will be procured by the site from commercial sources.**

8.7.1 Dose Modification of Standard of Care Agents

- **All toxicities that occur during the study will be actively managed following medical standard of care unless otherwise specified in the protocol.**
- **Toxicities should be attributed, whenever possible, to a specific drug (TAK-079 study drug, or standard chemotherapy agents pomalidomide or dexamethasone, as applicable) so that dose modifications can be made rationally. Reduction of 1 agent and not others is appropriate if toxicity is considered to be related primarily to one of the agents. If multiple toxicities are attributed to an individual agent (study drug or standard chemotherapy agent), dose adjustments should be made according to the guidelines for the most severe toxicity.**
- **Toxicities attributed to pomalidomide or dexamethasone, as applicable, should be managed according to the relevant guidelines in the respective product information [20,28].**
- **Once dose reduction has been implemented, unless otherwise stated specifically in the relevant product information and after discussion with the Sponsor Study Clinician (or designee), dose re-escalation should not occur.**

8.9 ~~8.6~~ 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 received until 30 days after the final dose will be recorded in the electronic case report forms (eCRFs) (note additional information in Section 9.4.9 and Appendix A).
- The following medications and procedures are permitted while the patient is receiving the study drug:
  - **For patients in the Combination Cohort (TAK-079–PomDex) only: patients must adhere to the pregnancy prevention program (Pomalyst REMS).**
  - **For patients in the Combination Cohort (TAK-079–PomDex) only: patients receiving pomalidomide should be on routine thromboprophylaxis according to product label, published guidelines, and institutional practice [20,29].**
  - Systemic corticosteroid use ≤10 mg/day (prednisone or equivalent).

– Myeloid growth factors (eg, granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice. **However, myeloid growth factors will not be allowed in Cycle 1 unless the study is in the expansion phase as their prophylactic use can interfere with DLT determination.**

– Transfusions with RBCs and platelets as clinically indicated; ~~localized~~**however, platelet use will not be allowed in Cycle 1 unless the study is in the expansion phase because their prophylactic use can interfere with DLT determination.**

– **Localized** radiation for pain management for osteolytic lesions.

– …

8.10 ~~8.7~~ Precautions and Restrictions

An interference with serological testing has been described with the anti-CD38 antibody daratumumab [23]. Daratumumab binds to CD38 on RBCs and results in a positive indirect antiglobulin test (Indirect Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not affected. It is possible TAK-079 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 TAK-079. 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.

Fluid ~~deficit~~**deficits** should be corrected before initiation of treatment and during treatment.

- …..
- 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 at least 90 days or 5 half-lives after the last dose of study drug (whichever is longer)~~,~~**. Note the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [30,31], a conservative time frame to continue contraception would be 150 days.** OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

[redacted]

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug~~.~~**. Note the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 immunoglobulins as well as other IgG1 human monoclonal antibodies [30,31], a conservative timeframe to continue contraception would be 150 days.** OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

For men and women patients enrolled in the Combination (TAK-079–PomDex) Cohort only: patients receiving pomalidomide must adhere to the Pomalyst REMS requirements per the product label [20].

In addition, a close monitoring of serum chemistry, particularly creatinine, potassium, and uric acid levels must be performed. Patients with tumor lysis syndrome should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis as indicated).

8.11 ~~8.8~~ Management of Specific Adverse Reactions

8.11.3 ~~8.8.3~~ Handling of Low Platelet Counts

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For patients in the phase 1 Combination Cohort, thrombocytopenia is a known TEAE reported with pomalidomide and should be monitored and managed according to the product information [20].

8.11.4 ~~8.8.4~~ Risk of Infection

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For patients in the phase 1 Combination Cohort, neutropenia is a known adverse drug reaction reported with pomalidomide and should be monitored and managed according to the product information [20].

8.16 ~~8.13~~ Storage, Handling, and Accountability

8.16.1 ~~8.13.1~~ Storage and Handling

….

During shipping, vials will be protected from light and ~~maintained below -15°C (5°F)~~**shipped as noted in the pharmacy manual**. Each TAK-079 shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

[redacted]

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area ~~must~~**should** be maintained every day.

…

8.18 Standard Drug Procurement Procedures: Patients in the Combination Cohort Only

8.18.1 Pomalidomide

Pomalidomide will be procured by the site from commercial sources. Additional details are provided in the product information [20]. Patients receiving pomalidomide must adhere to the Pomalyst REMS program per the product label.

Pomalidomide capsules should be stored at temperatures in accordance with the instructions provided in the manufacturers product information.

8.18.2 Dexamethasone

Dexamethasone will be procured by the site from commercial sources. Additional details are provided in the product information (Decadron USPI).

Dexamethasone tablets should be stored according to the instructions provided in the manufacture's product information.

8.19 Other Protocol-Specified Materials

TAK-079 will be supplied for use in this clinical study. No other drugs (including PomDex in the Combination Cohort) or ancillary materials are supplied for use in this study.

9.3 Treatment Group Assignments

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For phase 1 Combination Cohort (TAK-079–PomDex) Cohort only: patients must meet prespecified inclusion/exclusion criteria in Section 7.0 to be assigned to this cohort.

9.4 Study Procedures

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Patients receiving pomalidomide in the Combination Cohort (TAK-079–PomDex) must adhere to the Pomalyst REMS program per the product label. Pregnancy tests may also be repeated during the study as per request of the IEC/IRBs or required by local regulations.

9.4.12 ECG

...

The triplicate ECG measurements should be completed before the PK blood draw. Collection of triplicate ECGs should ~~begin after the patient has rested in supine position for approximately 5 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of each other and over a 10-minute window. It is recommended that patients refrain from eating or limit~~

~~themselves to bland food for 1 hour before dosing and for 1 hour before each scheduled triplicate ECG measurement~~**be done according to institutional standards**.

….

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters ~~shown in Table 9.a~~ and urine ~~samples~~**sample parameters** for analysis ~~of the parameters~~**are** shown in ~~Table 9.b~~**the tables below. Samples** will be obtained as specified in the SOE (Appendix A). They will be performed locally only.

For Patients in Cohorts Receiving TAK-079 monotherapy:

Table 9.a Clinical Chemistry and Hematology Tests for Research Purposes

Hematology	**Serum Chemistry**	
ANC	Albumin	Creatinine clearance
Hematocrit	ALP	CRP
Hemoglobin	ALT	Glucose (nonfasting)
Platelet (count)	AST	GGT
Reticulocyte count	Bilirubin (total)	LDH
RBC count	BUN	Phosphate
WBC count	Calcium	Potassium
~~WBC~~ with differential	Chloride	Sodium
Coagulation panel	CO_2 (bicarbonate)	Total protein
	Creatinine	Urate (uric acid)

ALP=: alkaline phosphatase; ALT=: alanine aminotransferase; ANC=: absolute neutrophil count; AST=: serine aminotransferase; BUN=: blood urea nitrogen; CRP=: C-reactive protein; GGT=: γ-glutamyl transferase; LDH=: lactate dehydrogenase; RBC=: red blood cell; WBC=: white blood cell.

Table 9.b Clinical Urinalysis Tests for Research Purposes

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

For estimation of creatinine clearance, the Cockcroft-Gault formula will be employed as follows:

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

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

[redacted]

For patients in the phase 1 Combination Cohort (TAK-079–PomDex) Cohort only:

Table 9.c Clinical Hematology and Chemistry: Standard of Care Laboratory Tests

Hematology	Chemistry	
Leukocytes with complete differential (total neutrophils [ANC], lymphocytes, monocytes, eosinophils, and monocytes)	Albumin	CO_2 (bicarbonate)
Platelet count	ALP	Creatinine
Hemoglobin	ALT	Estimated glomerular filtration rate
Serum pregnancy test	AST	Glucose
	B2- microglobulin	LDH
	Bilirubin (direct and indirect)	Potassium
	Calcium	Sodium
	Chloride	Urate

ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: serine aminotransferase; LDH: lactate dehydrogenase.

Table 9.d Clinical Hematology and Chemistry: Tests for Research Purposes

Clinical Hematology or Chemistry	Serology antibody titers
Coagulation panel (PT, PTT, INR)	Hepatitis B
Indirect and direct coombs	Hepatitis C
C-reactive protein	HIV

INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time.

Table 9.e Clinical Urinalysis: Tests for Research Purposes

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity, appearance, and color
Nitrite	Urobilinogen
Occult blood	Microscopic assessment (a)

(a) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals.

All procedures and tests should be done as outlined in the SOE (Appendix A). After 24 months on treatment, the patient may be monitored according to standard clinical practice per the treating physician.

9.4.14 Disease Response Assessments

Patients will be assessed for disease response according to the IMWG criteria ([~~17,18]; Appendix E).~~**21,22]; Appendix E). In addition, in patients that have myeloma measurable by serum**

free light chains, MR will be defined as a reduction of ≥25 but ≤49% in the difference between involved and uninvolved FLC levels.

For patients in the phase 1 Combination Cohort (TAK-079–PomDex) Cohort only:

Table 9.f Myeloma Disease Assessments: Tests Standard of Care Tests

Serum/Urine	Bone Marrow/Imaging
SPEP	Bone marrow biopsy and/or aspirate [(a)]
UPEP	Cytogenetics [presence of del (17), t(4:14), and t(14:16) at a minimum]
Immunofixation (serum and urine)	Imaging (skeletal survey, CT scan, PET/CT scan, MRI)
Quantification immunoglobulin levels	
Serum FLC	

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.
(a) The BMAs only at Cycle 2D1, C4D1, C7D1, and C13D1 are for research purposes unless these align with a suspected CR then this procedure would be Standard of Care.

For all patients:

After 24 cycles on treatment, the patient may be monitored according to standard clinical practice per the treating physician.

9.6 Completion of Study (for Individual Patients)

…

It is anticipated that the duration of the study will be approximately ~~36~~**42** months (~~3~~**3.5** years).

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

13.1.1 Analysis Sets

All-enrolled analysis set: The all-enrolled analysis set will include all patients enrolled into the study, regardless of whether they received any dose of ~~TAK-079.~~**any study drug.**

…

Safety analysis set: The safety analysis set will include all enrolled patients who receive at least 1 dose of ~~TAK-079.~~**any study drug.**

…

13.1.3 Efficacy Analysis

…

The preliminary efficacy of TAK-079 for MM will be evaluated by measuring the ORR **(**defined as the proportion of patients who achieved a PR or better during study~~,~~**) and** the composition of

[redacted]

sCR, CR, VGPR, and PR as defined by the IMWG Uniform Response Criteria (see **Appendix E). In addition, MR will be analyzed (see Section 9.4.14 and** Appendix E).

...

13.3 Determination of Sample Size

It is expected that approximately ~~42~~**100** patients will be enrolled in total for phase 1 and 2a combined. Once the RP2D is determined in phase 1, approximately ~~18~~**48** patients will be treated in phase 2a to provide a preliminary estimate of the ORR in patients with RRMM.

A 3+3 dose escalation schema will be used for dose escalation as described in Section 8.3.2.

A group of 3 to 6 patients will be enrolled in each TAK-079 dose cohort based on safety, clinical, PK, [redacted] data. Each patient will participate in only 1 dose cohort. The actual dose levels may be adjusted based on the observed safety profile.

Additional patients may be enrolled in a limited cohort expansion to confirm the safety and [redacted] before the phase 2a of this study is opened to enrollment. ~~Approximately 6 dose levels are planned. For phase 1, the number of patients is planned to be approximately 24.~~**In the phase 1 dose Confirmatory Cohort, approximately 18 patients will be enrolled at 1 dose and schedule: 12 patients with RRMM that is anti-CD38 naive and up to 6 patients with RRMM that is refractory to an anti-CD38 therapy. In the Combination Cohort, approximately 18 patients with RRMM that has been previously treated with at least 2 prior therapies and that is refractory to the last therapy will be enrolled.**

In phase 2a, up to a total of ~~18~~**48** patients will be treated to provide a preliminary estimate of the ORR in **2 expansion cohorts of** patients with RRMM~~. All~~**: up to 24** patients ~~must show a clear evidence of PD~~ with **RRMM that is anti-CD38 naive and up to 24 patients with RRMM that is refractory to an** anti-CD38 therapy. Phase 2a of the study will also provide a more robust estimate of the safety profile to determine whether the MTD is appropriate for future studies as the RP2D.

No prospective calculations of statistical power have been made; however, Table 13.a shows the width of the 80% CI, based on the observed ORR in a cohort size of ~~18~~**24** patients, for a range of observed response rates. ~~An observed ORR greater than 20% would be of interest in this relapse/refractory population.~~

Table 13.a 80% Confidence Interval Based on the Observed ORR

[redacted]

N =~~18~~ **24** patients.
ORR~~=~~**:** overall response rate.

[redacted]

16.0 REFERENCES

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[redacted]

Appendix A Schedule of Events

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screen-ing (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Informed consent (b)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
HBV, HCV, and HIV	X								
Height and weight (c)	X	X				X			
ECOG performance status	X	X				X			
ECG (d)	X	X				X			
		ECG measurements additionally on **Days 2, 3**, and **4** for Cycles 1 and 2 (see Section 9.4.12).							
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).								
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).								
Dosing for Phase 1 Dose Escalation Cohort									
Pre-injection medication		X	X	X	X	X	X	X	X
TAK-079 injection (f)		X	X	X	X	X	X	X	X
Dosing Patients in Dose Confirmation Cohort									
Pre-injection medication		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TAK-079 SC injection (f)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dosing Patients in Combination Cohort Only									

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screen-ing (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Pre-injection medication		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TAK-079 SC injection (f)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pomalidomide		**Day 1-21 in each cycle**							
Dexamethasone		**Day 1, 8, 15, and 22 in each cycle**							
Laboratory assessments									
Serum chemistry (g)	X	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X	X
Urinalysis (i)	X	X				X			
Pregnancy test (j) (k)	X	X				X			
Response assessments for MM									
Investigator disease assessment (t)						X			
Serum M-protein	X	X				X			
Urine M-protein (l)	X	X				X			
Serum FLC assay (m)	X	X				X			
Immunofixation - serum and urine (n)	X	X				X			
Quantification of Ig	X	X				X			
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)	X								
Biological assessments									
Bone marrow aspiration (BMA) (p)	X					X			
Serum sample for TAK-079 PK (q)		X	X	X	X	X	X	X	X
		PK sampling additionally on **Days 2, 3**, and **4** for Cycles 1 and 2.							

[redacted]

Screening, Baseline, Treatment Period Cycles 1 and 2

Study Period (Phases 1 and 2a)	Screening (a)	Treatment Phase (Weekly)							
		Cycle 1				Cycle 2			
Cycle Day		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**
Window Allowed		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Serum sample for immunogenicity (ADA/titer) (s)		X		X		X			
Serum sample for direct and indirect Coombs test	X	X				X			

Footnotes appear on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 3 Through 6

Study Period (Phases 1 and 2a)	Treatment Phase (Every 2 Weeks)							
	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Height and weight (c)	X		X		X		X	
ECOG performance status	X		X		X		X	
ECG (d)	X		X		X		X	
Physical examination	X	X	X	X	X	X	X	X
Vital signs (e)	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.							
AE reporting	Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3).							
	SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).							
Dosing Patients in Dose Escalation Cohort								
Pre-injection medication	X	X	X	X	X	X	X	X
TAK-079 injection (f)	X	X	X	X	X	X	X	X
Dosing Patients in Dose Confirmation Cohort								
Pre-injection medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TAK-079 SC injection (f)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dosing Patients in Combination Cohort Only								
Pre-injection medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
TAK-079 SC injection (f)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pomalidomide	**Day 1-21 in each cycle**							
Dexamethasone	**Day 1, 8, 15, and 22 in each cycle**							
Laboratory assessments								
Serum chemistry (g)	X	X	X	X	X	X	X	X
Hematology (h)	X	X	X	X	X	X	X	X

[redacted]

Treatment Period Continued: Cycles 3 Through 6

Study Period (Phases 1 and 2a)	Treatment Phase (Every 2 Weeks)							
	Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle Day	**C3D1**	**C3D15**	**C4D1**	**C4D15**	**C5D1**	**C5D15**	**C6D1**	**C6D15**
Window Allowed	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**
Urinalysis (i)	X		X		X		X	
Pregnancy test (j) (k)	X		X		X		X	
Response assessments for MM								
Investigator disease assessment (t)	X		X		X		X	
Serum M-protein	X		X		X		X	
Urine M-protein (l)	X		X		X		X	
Serum FLC assay (m)	X		X		X		X	
Immunofixation - serum and urine (n)	X		X		X		X	
Quantification of Ig	X		X		X		X	
Skeletal survey: WB x-ray, CT, low-dose CT, PET-CT, or MRI scan (o)							X	
Biological assessments								
Bone marrow aspiration (BMA) (p)			X					
Serum sample for TAK-079 PK (q)	X	X	X	X	X	X	X	X
[redacted]								
Serum sample for immunogenicity (ADA/titer) (s)	X		X		X		X	
Serum sample for direct and indirect Coombs test	X		X		X		X	

Footnotes appear on last page of SOE tables.

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	**C7D1**	**C8D1, CXD1**	**Up to 30 days After Last Dose**	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Laboratory assessments					
Height and weight (c)	X	X	X		
ECOG performance status	X	X	X		
ECG (d)	X	X	X		
Physical examination	X	X	X		
Vital signs (e)	X	X	X		
Monitoring of concomitant medication and procedures **AE reporting**	Recorded from up to 21 days before the first dose of TAK-079 through 30 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first. Recorded from signing of the ICF through 30 days after the last dose of study drug (Section 10.3). SAEs (includes pretreatment, and related and unrelated treatment-emergent events) will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (Section 10.3).				
~~AE reporting~~					
Dosing Patients in Dose Escalation Cohort					
Pre-injection medication	X	X			
TAK-079 injection (f)	X	X			
Dosing Patients in Dose Confirmation Cohort					
Pre-injection medication	**X**	**X**			
TAK-079 SC injection (f)	**X**	**X**			
Dosing Patients in Combination Cohort Only					
Pre-injection medication	**X**	**X**			
TAK-079 SC injection (f)	**X**	**X**			
Pomalidomide	**Day 1-21 each cycle**				
Dexamethasone	**Day 1, 8, 15, and 22 each cycle**				

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

Study Period (Phases 1 and 2a)	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
	Cycle 7	Cycle 8 and beyond	EOT/Early Termination	PFS Follow-Up Every 4 Weeks	OS Follow-Up Every 12 Weeks
Cycle Day	**C7D1**	**C8D1, CXD1**	**Up to 30 days After Last Dose**	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Laboratory assessments					
Serum chemistry (g)	X	X	X		
Hematology (h)	X	X	X		
Urinalysis (i)	X	X	X		
Pregnancy test (j) (k)	X	X	X		
Response assessments for MM					
Investigator disease assessment (t)	X	X	X	X	
Serum M-protein	X	X	X	X	
Urine M-protein (l)	X	X	X	X	
Serum FLC assay (m)	X	X	X	X	
Immunofixation - serum and urine (n)	X	X	X		
Quantification of Ig	X	X	X		
Skeletal survey: WB X-ray, CT, low dose CT, PET-CT, or MRI scan (o)			X		
Biological assessments					
Bone marrow aspiration (BMA) (p)	X	X (Cycle 13 only)			
Serum sample for TAK-079 PK (q)	X	X	X		
[redacted]					
Serum sample for immunogenicity (ADA/titer) (s)	X	X	X		
Serum sample for direct and indirect Coombs test	X	X	X		

[redacted]

Treatment Period Continued: Cycles 7 to Follow-up and Overall Survival Follow-up

	Treatment Phase (Monthly; Every 4 Weeks; to PD)			Follow-Up Phase	
Study Period (Phases 1 and 2a)	**Cycle 7**	**Cycle 8 and beyond**	**EOT/Early Termination**	**PFS Follow-Up Every 4 Weeks**	**OS Follow-Up Every 12 Weeks**
Cycle Day	**C7D1**	**C8D1, CXD1**	**Up to 30 days After Last Dose**	--------	--------
Window Allowed	**±2 days**	**±2 days**	**±7 days**	**± 7 days**	**± 7 days**
Subsequent anticancer therapy				X	X
Survival (u)					X

Footnotes begin on the next page.

[redacted]

ADA=: antidrug antibody; AE=: adverse event; BMA=: bone marrow aspirate; [redacted]; C=: cycle; CR=: complete response; CT=: computed tomography; CXD1=: Day 1 of additional treatment cycles (ie, after Cycle 8); D=: day; ECG=: electrocardiogram; ECOG=: Eastern Cooperative Oncology Group; EOT=: end of treatment; FLC=: free light chain; HBV=: hepatitis B virus; HCV=: hepatitis C virus; ICF=: Informed Consent Form; Ig=: immunoglobulin; IMWG=: International Myeloma Working Group; IR=: injection reaction; MM=: multiple myeloma; MRI=: magnetic resonance imaging; OS=: overall survival; PD=: disease progression; PET-CT=: positron emission tomography-computed tomography; PFS=: progression-free survival; PK=: pharmacokinetics; PR=: partial response; RBC=: red blood cell; SAE=: serious adverse event; SOE=: Schedule of Events; [redacted]; VGPR=: very good partial response; WB=: whole body; WBC=: white blood cell.

(a) The screening period is 21 days (ie, Days -21 to Day -1).
(b) Written informed consent must be obtained before performing any protocol-specific procedure.
(c) Height will be measured only at the screening visit. Weight will be measured at indicated visits.
(d) A single ECG will be collected at the screening visit. PK time-matched triplicate 12-lead ECGs will be collected during Cycles 1 and 2, as specified in Appendix B. Single 12-lead ECGs will be administered for all other designated visits (ie, after Cycle 2).
(e) Vital signs are measured prior to TAK-079 injection. Blood pressure will also be measured before starting each 2 mL injection, and at any time the patient complains of symptoms consistent with IR. Vital signs include temperature, pulse, respiratory rate, and blood pressure.
(f) Time and anatomical site should be recorded for each injection (see Figure 6.a and Section 8.0).
(g) Serum β_2 microglobulin levels will be measured at screening only. Refer to Section 9.4.13.1 for a list of clinical chemistry laboratory assessments.
(h) Refer to Section 9.4.13.1 for a list of hematology laboratory assessments.
(i) Microscopic analyses will be performed only as clinically indicated: bacteria, RBCs, WBCs, casts, and crystals. Refer to Section 9.4.13.1 for a list of urinalysis assessments.
(j) Pregnancy test (Refer to Section 9.4.8): Women of childbearing potential must have 2 negative pregnancy tests prior to starting study drug. A serum pregnancy test will be performed during screening (within 10-14 days before start of study drug). A serum pregnancy test is required within 24 hours before start of study drug.
(k) Pregnancy test (refer to Section 9.4.8): On-treatment: a urine pregnancy test is required at designated study visits. A urine pregnancy test is required at the follow-up visit in women of childbearing potential. If menstrual period is delayed, absence of pregnancy in women of childbearing potential must be confirmed by serum pregnancy test.
(l) Sampling required only if urine M-protein is measurable at Day 1 (visit 2). Per IMWG, required in all patients for PR, VGPR, CR, at EOT, and to determine PD during PFS follow-up.
(m) Blood sample obtained for the serum FLC assay to include quantification of kappa and lambda chains and ratio). To be analyzed locally.
(n) Will also be collected to confirm a CR.
(o) May be performed up to 21 days before first dose of TAK-079. Additional surveys (x-ray, CT, or MRI) may be performed at the investigator's discretion, eg, in case of bone pain. If disease is documented, then a repeat scan should be performed as required to document a response or PD.
(p) BMAs: [redacted] At screening, a standard BMA drawn prior to consent is acceptable provided this is collected within 5 weeks before the first dose; cytogenetics will be done locally (See Section 9.4.14.6).
For response assessment purposes, when a CR is suspected based on laboratory values, a BMA is required to confirm a CR. At the time of this procedure (at CR), 1 aspirate sample is analyzed locally for evaluation of disease, [redacted]
(q) Blood samples for PK characterization will be collected at time points specified in Appendix B PK Sampling Schedule.
[redacted]

[redacted]

(s) Serum samples for immunogenicity assessment will be collected at baseline (before TAK-079 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.
(t) Patients who discontinue treatment for reasons other than PD will continue to be followed every 4 weeks until PD, death, start of subsequent anticancer therapy, study termination, or 12 months after discontinuation of study treatment, whichever occurs first.
(u) Patients will be followed every 12 weeks until death, loss to follow-up, consent withdrawal, or study termination.

[redacted]

Appendix E IMWG Criteria

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IMWG Uniform Criteria for Response [~~17,18,24~~21,22,33]

Category of Response	Response Criteria
sCR	Criteria for CR as defined below, with the addition of a normal FLC ratio, and an absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry; 2 consecutive assessments of laboratory parameters are needed (a).
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; 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; 2 consecutive assessments are needed (b).
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 >4 colors).
Molecular CR	CR as defined, plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5}).
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours; 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; 2 consecutive assessments are needed (c).
PR	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed (a) no known evidence of progressive or new bone lesions if radiographic studies were performed.
Minimal response (MR) (b)	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above criteria, if present at baseline, 25% to 49% reduction in the 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). **In this study, in patients that have myeloma measurable by serum free light chains, MR will be defined as a reduction of ≥25 but ≤49% in the difference between involved and uninvolved FLC levels.**
SD (c)	Does not meet the response criteria for CR (any variant), VGPR, PR, MR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

[redacted]

Source: Rajkumar SV et al, 2011 and Palumbo A et al, 2014 [~~17,18~~**21,22**]~~.~~
CR=**:** complete response; FLC=**:** free light chain; IMWG=**:** International Myeloma Working Group; MR=**:**minimal response; ORR=**:** overall response rate; PR=**:** partial response; sCR=**:** stringent complete response; SD=**:** stable disease; VGPR=**:** very good partial response.
(a) Clonality should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
(b) For relapse-refractory myeloma only.
(c) These categories do not contribute to the ORR.

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[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	02-Apr-2019 13:18 UTC
[redacted]	Clinical Science Approval	02-Apr-2019 14:14 UTC
[redacted]	Clinical Science Approval	02-Apr-2019 14:18 UTC