Clinical Study Protocol

NCT Number: NCT05556616

Title: A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of Intravenous Modakafusp Alfa as Part of Combination Therapy in Adult Patients With Multiple Myeloma

Study Number: TAK-573-1502

Document Version and Date: Amendment 5 US v1, 19 September 2024

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

PROTOCOL

A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of Intravenous Modakafusp Alfa as Part of Combination Therapy in Adult Patients With Multiple Myeloma

Sponsor: Takeda Development Center Americas, Inc
500 Kendall Street
Cambridge, MA 02142 USA

Study Number: TAK-573-1502

Abbreviated EudraCT Number: 2022-001418-20

ClinicalTrials.gov Identifier: NCT05556616

Compound: Modakafusp alfa (TAK-573)

Date: 19 September 2024 **Amendment Number:** 5 US v1

Amendment History:

Date	Amendment Number	Amendment Type	Region
19 September 2024	Amendment 5 US v1	Substantial; Regional	United States
03 April 2024	Amendment 4 v2	Substantial	Global
28 February 2024	Amendment 4 v1 (not implemented)	Substantial	Global
13 June 2023	Amendment 3	Substantial	Global
17 August 2022	Amendment 2	Substantial	Global
27 May 2022	Amendment 1	Substantial	Global
13 May 2022	Initial protocol EU v1	Nonsubstantial; Regional	European Union
01 April 2022	Initial protocol	Not applicable	Global

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

CONFIDENTIAL PROPERTY OF TAKEDA

This document is a confidential communication of Takeda. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site, which includes the names and contact information for the medical monitor and responsible medical officer.

Serious adverse event (SAE) and pregnancy reporting information is presented in this protocol in Sections 10.2 and 10.4, respectively, and in the Investigator Site File (ISF). Information on reporting product complaints is in the pharmacy manual.

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

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

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 in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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

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

[redacted] MD (or designee) Date

[redacted]

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix D).

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

1.3 Protocol Amendment 5 US v1 Summary of Changes

Protocol Amendment 5 US v1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 5 US v1. The primary reason for this amendment was to include the United States (US) Food and Drug Administration (FDA) recommendation of excluding patients with a high risk of bleeding events, including those on anticoagulation [redacted]

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

A summary of changes for all prior protocol amendments is found in Appendix J.

Protocol Amendment 5 US v1			
Summary of Changes Since the Last Implemented Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	[redacted]	[redacted]	Revised per FDA recommendation
2.	7.2 Exclusion Criteria	Added exclusion criterion #18: "Patient has a high risk of hemorrhage such as uncontrolled chronic bleeding disorder or is currently being treated with therapeutic anticoagulation. Antithrombotic prophylaxis for lenalidomide and pomalidomide is authorized."	Revised per FDA recommendation

FDA: Food and Drug Administration; TEAE: treatment-emergent adverse event.

Property of Takeda: For non-commercial use only, use subject to the applicable Terms of Use

TABLE OF CONTENTS

Property of Takeda For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

LIST OF IN-TEXT TABLES

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

LIST OF IN-TEXT FIGURES

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

LIST OF APPENDICES

LIST OF APPENDIX TABLES

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc	**Compound:** Modakafusp alfa (TAK-573)
Title of Protocol: A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of Intravenous Modakafusp Alfa as Part of Combination Therapy in Adult Patients With Multiple Myeloma	**EudraCT No:** 2022-001418-20 **ClinicalTrials.gov Identifier:** NCT05556616
Study Number: TAK-573-1502	**Phase:** 1b

Study Design:

This is a global multicenter, open-label, phase 1b study designed to evaluate the safety and tolerability of modakafusp alfa in combination therapy and to determine the recommended phase 2 dose (RP2D) of the combination therapy with modakafusp alfa in adult patients with multiple myeloma (MM).

The study will be conducted in 3 groups:

Group 1: MM in maintenance therapy.

Group 2: Relapsed/refractory multiple myeloma (RRMM) doublets.

Group 3: RRMM triplets.

These groups will consist of 1 or more of the following combination therapy arms:

Group 1: The MM maintenance combination will consist of a dose escalation/de-escalation of modakafusp alfa and lenalidomide guided by Bayesian Optimal Interval (BOIN) design. This group is designed to determine the recommended dose of modakafusp alfa in combination with lenalidomide as maintenance therapy in MM after autologous stem cell transplantation (ASCT).

- Arm 1: Modakafusp alfa intravenous (IV) infusion in combination with lenalidomide orally (PO).

Group 2: The RRMM doublet combinations, as listed below, will consist of a dose escalation/de-escalation of multiple doublet combination arms guided by BOIN design. The doublet combinations are designed to determine the recommended dose of modakafusp alfa with combination agents including, but not limited to, bortezomib and pomalidomide. Data will inform decisions regarding the respective triplet combination escalation/de-escalation starting doses.

- Arm 2 modakafusp alfa + pomalidomide: Modakafusp alfa IV infusion in combination with pomalidomide PO.
- Arm 3 modakafusp alfa + bortezomib: Modakafusp alfa IV infusion in combination with bortezomib subcutaneous (SC).
- Arm 4 modakafusp alfa + carfilzomib: Modakafusp alfa IV infusion in combination with carfilzomib IV (*closed to enrollment*).

Group 3: The RRMM triplet combinations, as listed below, will consist of a dose escalation/de-escalation phase of multiple triplet combination arms guided by the doublet combination data, modakafusp alfa/daratumumab data from TAK-573-2001, and BOIN design. The triplet combinations are designed to determine the RP2D of modakafusp alfa with the 2 associated combination agents, thereby defining the triplet therapy dose.

- Arm A modakafusp alfa + pomalidomide + bortezomib: Modakafusp alfa IV infusion in combination with bortezomib SC and pomalidomide PO.
- Arm D modakafusp alfa + daratumumab + pomalidomide: Modakafusp alfa IV infusion in combination with pomalidomide PO and daratumumab SC.

Duration of Study

The treatment cycle duration is 28 days. Patients in Group 1 (MM maintenance) who are minimal/measurable residual disease (MRD)-negative (MRD[-]) may continue to receive modakafusp alfa in combination with lenalidomide until disease progression, unacceptable toxicity, or a maximum of 2 years for MRD[-] patients,

Property of Takeda For non-commercial use only and subject to the applicable Terms of Use

whichever occurs first. Patients who remain MRD-positive with demonstrated clinical benefit after 2 years of maintenance therapy may continue treatment beyond 2 years with agreement of the sponsor/designee. Patients in Groups 2 and 3 (RRMM doublets and RRMM triplets) may receive modakafusp alfa in combination with associated agents until disease progression, unacceptable toxicity, or until any other discontinuation criterion is met (Section 9.11), whichever occurs first.

The follow-up phase of the study begins once a patient discontinues study treatment and completes the end-of-treatment visit; study follow-up continues until the study ends or the patient completes overall survival (OS) follow-up.

Primary Objectives

Group 1: MM Maintenance

- To determine the safety and tolerability of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with MM after ASCT.
- To determine the RP2D of the combination therapy with modakafusp alfa.

Group 2 and Group 3: RRMM Doublets and Triplets

- To determine the safety and tolerability of modakafusp alfa as part of either a 2- or 3-drug combination therapy in adult patients with RRMM.
- To determine the RP2D of the combination therapy with modakafusp alfa (recommended doses of the doublet or triplet combinations).

Secondary Objectives

Group 1: MM Maintenance

- To evaluate the preliminary efficacy of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with MM after ASCT.
- To evaluate rate and duration of MRD[-].
- To collect pharmacokinetic (PK) data to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

Group 2 and Group 3: RRMM Doublets and Triplets

- To evaluate the preliminary efficacy of modakafusp alfa as part of either a 2 or a 3-drug combination therapy in adult patients with RRMM.
- To evaluate rate and duration of MRD[-].
- To collect PK data of modakafusp to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

Patient Population: Patients aged 18 years or older with MM (Group 1) or RRMM (Groups 2 and 3).

Number of Subjects:	**Number of Sites:**
Approximately 120 patients will be enrolled. MM Maintenance: Approximately 18 patients (1 arm). RRMM Doublets: Approximately 66 patients. RRMM Triplets: Approximately 36 patients.	Approximately 50 sites globally.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Dose Level(s):	**Route of Administration:**
Modakafusp alfa: 60, 80 (starting dose), 120, and 240 mg Lenalidomide: 10 mg, 15 mg Pomalidomide: 2 mg, 3 mg, 4 mg Bortezomib: 1.3 mg/m^2 Daratumumab: 1800 mg	Modakafusp alfa: IV infusion Lenalidomide: PO Pomalidomide: PO Bortezomib: SC Daratumumab: SC
Duration of Treatment: For Group 1 (MM maintenance), patients may continue modakafusp alfa in combination with lenalidomide until disease progression, unacceptable toxicity, or a maximum of 2 years for MRD[-] patients, whichever occurs first. Patients who remain MRD positive with demonstrated clinical benefit after 2 years of maintenance therapy may continue treatment beyond 2 years with agreement of the sponsor/designee. For Group 2 and Group 3 (RRMM doublets and RRMM triplets), modakafusp alfa in combination with associated agents will be administered until disease progression or unacceptable toxicity, or until any other discontinuation criterion is met, whichever occurs first.	**Period of Evaluation:** 5 years

Main Criteria for Inclusion:

All patients in Group 1 (MM maintenance: modakafusp alfa/lenalidomide) only must have:

a) MM based on standard International Myeloma Working Group (IMWG) diagnostic criteria (Appendix G).

b) Undergone ASCT for the treatment of MM within 12 months of the start of induction therapy and completed ASCT within 180 days before enrollment (regardless of the lines of treatment). Consolidation cycles are allowed. Tandem transplant is allowed.

c) Not started lenalidomide maintenance before enrollment. Time to initiation of maintenance therapy: Patients may start maintenance therapy as early as 60 days after transplantation and up to 180 days after transplantation or consolidation.

d) MRD positive after ASCT (MRD assessed at threshold of 10^{-5} by local standard-of-care methods or central assessment, if a prior local MRD assessment had not been performed).

e) No prior progression after initial therapy (at any time before starting maintenance). Patients whose induction therapy was changed due to suboptimal response or toxicity will be eligible if they do not meet criteria for progression. In addition, no more than 2 regimens will be allowed before ASCT, excluding dexamethasone alone.

f) No prior allogeneic hematopoietic stem cell transplant or solid organ transplant.

g) Recovered to Grade ≤1 ASCT-related toxicities from the reversible effects of ASCT (except for alopecia and amenorrhea). MM based on standard IMWG diagnostic criteria.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

All patients in Group 2 and Group 3 (RRMM doublets and RRMM triplets) must have:

a) Measurable disease, defined as at least 1 of the following:

- Serum M-protein ≥0.5 g/dL (≥5 g/L) on serum protein electrophoresis.
- Urine M-protein ≥200 mg/24 hours on urine protein electrophoresis.
- Serum FLC assay result with an involved FLC level ≥10 mg/dL (≥100 mg/L), provided the serum FLC ratio is abnormal (per IMWG criteria).

b) A confirmed diagnosis of MM according to IMWG criteria (Appendix G) with documented disease progression in need of additional therapy as determined by the investigator.

c) For Group 2 RRMM doublet arms only: Patients who have received at least 3 prior lines of antimyeloma therapy, including at least 1 proteosome inhibitor (PI), 1 immunomodulatory drug (IMiD), and 1 anti-CD38 monoclonal antibody (mAb) drug, or who are triple refractory to a PI, and IMiD, and an anti-CD38 mAb drug regardless of the number of prior line(s) of therapy.

d) For Group 3 RRMM triplet arms only: Patients who have received 1 to 3 prior lines of antimyeloma therapy, including at least 1 PI and 1 IMiD, and who are not refractory* to the combination partners.

e) For anti-CD38 arms, forced expiratory volume in 1 second ≥50% predicted by pulmonary function testing.

NOTES:

A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens. (For example, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by a stem cell transplantation, consolidation, and maintenance is considered 1 line.)

* Refractory myeloma is defined as disease that is nonresponsive while the patient is receiving primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of PD while on therapy (Rajkumar et al. 2011).

Main Criteria for Exclusion:

1. The patient is currently participating in another MM interventional study.
2. The patient received previous treatment with modakafusp alfa.
3. The patient has a diagnosis of primary amyloidosis, Waldenström disease, monoclonal gammopathy of undetermined significance or smoldering MM per IMWG criteria or standard diagnostic criteria, plasma cell leukemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), lymphoplasmacytic lymphoma.
4. The patient has had another malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy and that in the opinion of the local investigator, with concurrence with the principal investigator, is considered cured with minimal risk of recurrence within 3 years.
5. The patient has evidence of central nervous system involvement and/or meningeal involvement due to MM exhibited during screening.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Endpoints:

The primary endpoints of the study for Groups 1, 2, and 3 (MM maintenance, RRMM doublets, and RRMM triplets) are occurrence of dose-limiting toxicities (DLTs) in Cycle 1 and frequency and severity of treatment-emergent adverse events (TEAEs).

Secondary endpoints are as follows:

Group 1 MM Maintenance: Progression-free survival (PFS); overall response rate (ORR) (per investigator assessment); duration of response (DOR); rate of MRD[-] at a threshold of 10^{-5} at 6 months, 1 year, and 2 years after treatment; duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-]; and antidrug antibody (ADA) incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).

Group 2 and Group 3 RRMM Doublets and Triplets: OS, ORR, PFS, time to progression (TTP), time to next treatment (TTNT), DOR, disease control rate (DCR), event-free survival (EFS), time to response (TTR), rate of MRD[-] complete response (CR) at a threshold of 10^{-5} with CR assessed by the investigator, rate of MRD[-] at a threshold of 10^{-5} , duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-], and ADA incidence and characteristics (eg, titer and specificity) and NAb.

Statistical Considerations:

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

Group 1: MM Maintenance: PFS will be analyzed using the safety analysis set and summarized using the Kaplan-Meier (KM) method. ORR will be analyzed using the response-evaluable analysis set, and rate of MRD[-] will be analyzed on the basis of the MRD analysis set. Both endpoints will be summarized with 2-sided 95% exact binomial CIs. Duration of MRD[-] will be analyzed in patients achieving MRD[-] using the KM method.

Group 2 and Group 3 RRMM Doublets and Triplets: ORR and DCR will be analyzed using the response-evaluable analysis set and summarized with 2-sided 95% exact binomial CIs. DOR and TTR will be analyzed for responders only. DOR will be summarized using KM method, and descriptive summary will be provided for TTR as a continuous variable. OS, PFS, EFS, TTP, and TTNT will be analyzed using the safety analysis set and summarized using KM method. Rate of MRD[-] CR will be analyzed for both the MRD-evaluable analysis set and the safety analysis set and summarized with 2-sided 95% exact binomial CIs. Rate of MRD[-] will be analyzed for the safety analysis set and summarized with 2-sided 95% exact binomial CIs. Duration of MRD[-] will be analyzed in patients achieving MRD[-] using KM method.

Sample Size Justification: The BOIN design will be implemented. The target toxicity rate for MTD is set to be $\phi = 0.25$ for MM maintenance and RRMM doublets and $\phi = 0.33$ for RRMM triplets. Patients will be enrolled and treated in cohort sizes of approximately 3. It is estimated that a total of approximately 120 DLT-evaluable patients will be enrolled : approximately 18 for MM maintenance (Arm 1), approximately 66 for RRMM doublet combinations, and approximately 36 for RRMM triplet combinations. Please see Appendix I for further details.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

3.0 STUDY REERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those performed by the study vendors. The identified vendors will perform specific study-related activities in full or in partnership with the sponsor.

3.2 Principal/Coordinating Investigator

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

3.3 List of Abbreviations

List of Abbreviations

ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBs	antibodies to hepatitis B surface antigen
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
auto-HSCT	autologous hematopoietic stem cell transplantation
BIW	twice weekly
BMA	bone marrow aspirate, bone marrow aspiration
BOIN	Bayesian Optimal Interval
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
DVd	bortezomib in combination with daratumumab and dexamethasone
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram electrocardiographic
ECOG	Eastern Cooperative Oncology Group
eConsent	electronic consent
EDC	electronic data capture
eCRF	electronic case report form
EFS	event-free survival
EOT	end-of-treatment
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FLC	free light chain
FVC	forced vital capacity
GCP	Good Clinical Practice

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

List of Abbreviations

G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN	interferon
IFN-α	interferon alpha
IFN-α2b	interferon alpha 2b
IFNAR	interferon alpha receptor
IFN-γ	interferon gamma
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IP	intraperitoneal(ly)
IRB	institutional review board
IRR	infusion-related reaction
ISF	Investigator Site File
IV	intravenous(ly)
IVIG	intravenous immunoglobulins
K_D	binding affinity
KM	Kaplan-Meier
mAb	monoclonal antibody
MDP	modakafusp alfa + daratumumab + pomalidomide
MedDRA	Medical Dictionary for Regulatory Activities
MK	modakafusp alfa + carfilzomib
MKP	modakafusp alfa + carfilzomib + pomalidomide
MM	multiple myeloma
MP	modakafusp alfa + pomalidomide
MPV	modakafusp alfa + pomalidomide + bortezomib
MRD	measurable/minimal residual disease
MRD[-]	measurable/minimal residual disease-negative, measurable/minimal residual disease negativity
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MV	modakafusp alfa + bortezomib
NAb	neutralizing antibody
NCI	National Cancer Institute

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

List of Abbreviations

NDMM	newly diagnosed multiple myeloma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	oral(ly)
PR	partial response
PTA	posttrial access
Q3W	every 3 weeks
Q4W	every 4 weeks
QD	once daily
RBC	red blood cell
REMS	Risk Evaluation and Mitigation Strategy
RP2D	recommended phase 2 dose
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAR	serious adverse reaction
SC	subcutaneous(ly)
sCR	stringent CR
SOC	standard-of-care
SOE	schedule of events
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
SVd	bortezomib/selinexor/dexamethasone
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiography
TNF-α	tumor necrosis factor alpha
TTNT	time to next treatment
TTP	time to progression
TTR	time to response

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

List of Abbreviations

UK	United Kingdom
UPEP	urine protein electrophoresis
US	United States
Vd	bortezomib in combination with dexamethasone
VGPR	very good partial response
VMP	bortezomib in combination with melphalan/prednisone

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

3.4 Corporate Identification

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

4.0 INTRODUCTION

4.1 Multiple Myeloma

Multiple myeloma (MM) is a plasma cell-derived malignancy characterized by bone lesions, hypercalcemia, anemia, and renal insufficiency that accounts for 10% of hematologic malignancies. According to statistics from the Global Cancer Observatory, there were an estimated 160,000 cases of MM globally in 2018. From 1990 to 2006, the global incidence of MM increased by 126% (Cowan et al. 2018). The incidence of MM is higher in male, black American, African American, and elderly populations. The median age at diagnosis is 69 years with only 3.1% of patients less than 45 years at diagnosis. It occurs slightly more frequently in males (8.8% in males versus 5.7% in females). MM incidence rate and mortality rate are twice as common in the black American and African American population compared with the white population (age-adjusted incidence rate and mortality rate of 13.8% and 6%, respectively, in the black American and African American population compared with 6.5% and 3%, respectively, among the white population (seer.cancer.gov/csr/1975_2018/, SEER Cancer Statistics Review, 1975-2018. National Cancer Institute, Bethesda, MD, Accessed March 15, 2022). This racial disparity is related to the higher prevalence of monoclonal gammopathy of undetermined significance in black American and African American populations (Rajkumar and Kumar 2016).

The 5-year survival rate of patients with MM is approximately 45% (Aletaha et al. 2008). MM persists as a mostly incurable disease because of its highly complex and diverse cytogenetic and molecular abnormalities (Chapman et al. 2011). The outcome for patients with MM patients has improved in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory drugs (IMiDs) (eg, lenalidomide), but patients whose disease becomes refractory or who are ineligible to receive bortezomib and IMiDs have an unfavorable prognosis (Kumar et al. 2012). Substantial progress in treatment has been made with recent approvals of biologic agents with newer mechanisms of action, such as anti-CD38 monoclonal antibody (mAb) drugs including daratumumab and isatuximab (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021; Sarclisa (Isatuximab) 2020), belantamab mafodotin (BCMA [B-cell maturation antigen]–targeting antibody drug conjugate) (Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021), and idecabtagene vicleucil (chimeric antigen receptor T-cell therapy) (Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021). Despite these recent advances, there is still a need for the development of novel targeted therapies that act in safe and effective ways against MM cells and are able to overcome certain limitations of current therapies.

4.2 Modakafusp Alfa (TAK-573)

4.2.1 Mechanism of Action

Modakafusp alfa is a first-in-class innate immunity enhancer that functions through the induction of targeted type I interferon (IFN) signaling in immune cells and MM cells. It is a recombinant humanized immunoglobulin (Ig)G4 anti-CD38 mAb fused to attenuated interferon alpha 2 beta

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

(IFN-α2b) that is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. The CD38 antibody portion of modakafusp alfa directs the attenuated interferon alpha (IFN-α) portion to CD38+ cells, thus achieving a high local concentration on IFN-α2b at the surface of these target cells. On CD38 cells, the attenuation results in approximately 130,000-fold reduced potency compared with IFN-α2b.

Modakafusp alfa binds with high affinity to human and cynomolgus CD38, with a binding affinity (K_D) of 168 pM and 1.25 nM, respectively (Report TPA-38-009). Modakafusp alfa can potently inhibit proliferation of CD38+ MM cells (half-maximal inhibitory concentration [IC_{50}] = 19.9 pM), whereas potency on CD38 nonexpressing (CD38) cells is approximately 2500-fold lower. The antibody portion of modakafusp alfa is an IgG_4 isotype (unlike the IgG_1 isotype of daratumumab) and is, therefore, unlikely to induce antibody-dependent cell-mediated cytotoxicity of normal CD38+ cells. Modakafusp alfa does not modulate the adenosine diphosphate-ribosyl cyclase activity of CD38, unlike daratumumab (Report TPA-38-045). IFN-α2b (Intron A), by comparison, has similar potency to modakafusp alfa on CD38+ cells (IC_{50} = 12.3 pM), but on CD38– cells, it is approximately 130,000-fold more potent than modakafusp alfa (half-maximal effective concentration [EC_{50}] ~0.37 pM).

Through the induction of targeted IFN signaling, modakafusp alfa activates innate and adaptive immune cells and elicits direct antiproliferative and apoptotic signals in MM cells, which have the potential to help patients with MM.

4.2.2 Targets

The tumor cell surface-expressed antigen CD38 is uniformly and highly expressed on MM cells (Lin et al. 2004; Santonocito et al. 2004) and at lower levels on various lymphoid and myeloid cells and some solid organs (Deaglio et al. 2001). Being highly expressed on the myeloma cell surface and not highly expressed on normal cells makes CD38 an appropriate target for antibodies conjugated with cytokines, radioisotopes (Green et al. 2014), or toxins (Bolognesi et al. 2005; Goldmacher et al. 1994). One cytokine of particular interest is IFN-α, which was used in MM as a maintenance treatment option following primary treatment and autologous or allogeneic stem cell transplantation. IFN-α shows direct inhibitory effects on some tumors, including myeloma, and it is a potent stimulator of both the innate and adaptive immune systems. However, systemic toxicity of IFN-α precludes the use of the cytokine at therapeutically effective doses for most patients. By reducing the K_D of IFN-α for its receptor, interferon alpha receptor (IFNAR), modakafusp alfa is expected to reduce binding of IFN-α to IFNAR on nontargeted, CD38– cells.

In contrast, binding of modakafusp alfa with high affinity via its CD38-targeting moieties is expected to increase the local concentration of attenuated IFN-α on CD38+ target cells, thereby inducing desired on-target IFNAR binding and subsequent IFN pathway activation. Additionally, IFN-α pathway activation induces upregulation of CD38 expression in malignant cells of patients with B-cell chronic lymphocytic leukemia (Bauvois et al. 1999), suggesting that modakafusp alfa may be able to increase CD38 target expression in MM and other CD38+ immune cells and thus

Property of Takeda. For non-commercial use only unless subject to the applicable Terms of Use

overcome the limitations seen with anti-CD38–depleting antibodies such as daratumumab. Modakafusp alfa increases CD38 expression on MM cells in vitro, which further supports this hypothesis (Report TPA-38-051).

CD38 is a multifunctional ectoenzyme involved in cell adhesion and transmembrane signaling. It is overexpressed in hematologic tumors, where it is believed to play a role in tumor cell migration and metastasis. CD38 has been reported to be highly expressed in 80% of MM patient-derived tumor cells (Lin et al. 2004). It is an approximately 45 kDa transmembrane glycoprotein expressed by immature hematopoietic cells, which is downregulated in mature cells and re-expressed at higher levels by activated lymphocytes such as T cells, B cells, dendritic cells, and natural killer (NK) cells (Funaro et al. 1990). Early bone marrow cells that are crucial for long-term (sustained) marrow recovery do not express CD38, but committed progenitor bone marrow cells, B cells in germinal centers, terminally differentiated plasma cells, and activated tonsils are CD38+ (Chillemi et al. 2013). Deaglio (Deaglio et al. 2008) reviewed the main tissues and cells where CD38 is present and these findings are summarized in Table 4.a. CD38 is also found in a soluble form in normal and pathological fluids (Funaro et al. 1996).

Table 4.a Reported Distribution of Human CD38

Tissue	Cellular Distribution	Putative Function
Bone marrow	Hematologic precursors plasma cells	Homing and apoptosis; marker of precursor cell commitment
Thymus	Throughout thymic development	Unknown
Spleen/lymph nodes	Germinal center B cells	Rescue from apoptosis
Blood	T, B, and natural killer cells, and monocyte subsets; platelets and erythrocytes; hematologic precursors plasma cells	Interaction with endothelium
Gut	Intra-epithelial and lamina propria lymphocytes	Mucosal immunity
Brain	Purkinje cells; neurofibrillary tangles	Memory process
Prostate	Epithelial cells	Unknown
Pancreas	β cells	Insulin secretion
Bone	Osteoclasts	Bone resorptions
Eye	Retinal cells	Vision process
Muscle	Sarcolemma of smooth and striated muscle	Muscle contraction

Source: (Deaglio et al. 2008).

4.2.3 Nonclinical and Toxicology Studies

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

4.2.3.1 Nonclinical Studies

4.2.3.1.1 Pharmacology Related to the Proposed Mechanism of Action

Modakafusp alfa effectively induces apoptosis in high-expressing CD38+ human myeloma cells as demonstrated in a caspase activation assay (EC_{50} = 23 pM); no apoptotic effects are observed with normal human peripheral blood mononuclear cells (PBMCs). Modakafusp alfa elicited a low level of cytokine release (tumor necrosis factor-alpha [TNF-α], interleukin (IL)-6, IL-8, interferon gamma [IFN-γ], and IL-2) from human PBMCs in vitro, less than or comparable to that reported with palivizumab (IgG1 against the respiratory syncytial virus).

In several human myeloma xenograft models, modakafusp alfa induced complete regressions at tolerable doses. A single modakafusp alfa dose of 10 mg/kg in the National Cancer Institute (NCI) H929 human myeloma xenograft model resulted in complete regression in all treated animals. In comparative xenograft studies, modakafusp alfa showed greater efficacy relative to established myeloma therapies, including bortezomib, lenalidomide, and daratumumab. Furthermore, under conditions of suboptimal activity of modakafusp alfa, strong synergy has been observed with other standard MM treatment agents such as bortezomib and lenalidomide.

4.2.3.1.2 Safety Pharmacology

No stand-alone safety pharmacology studies have been conducted with modakafusp alfa. However, in a Good Laboratory Practice (GLP) repeat-dose toxicity study in cynomolgus monkeys (Report DS-2015-055), central nervous system (CNS), cardiovascular, and respiration endpoints were included, in line with the ICH Guidance S6 (R1) for biotechnology products. No modakafusp alfa–related cardiovascular or CNS findings were identified at doses up to 30 mg/kg (the highest dose level tested). Increases in respiratory rate observed in the pivotal GLPcompliant repeat-dose study on Day 22 were attributed to effects secondary to the antidrug antibody (ADA) response.

4.2.3.1.3 PK and Product Metabolism in Animals

The PK of modakafusp alfa were characterized in CB17 SCID (severe combined immunodeficiency) mice bearing H929 human MM tumor and in cynomolgus monkeys. In mice, modakafusp alfa exhibited dose-proportional exposure following intraperitoneal (IP) injection at 3 and 10 mg/kg dose levels. The $t_{1/2}$ (terminal disposition phase half-life) of modakafusp alfa was 82 to 100 hours (Report TPA-38-021). In monkeys, modakafusp alfa exhibited a greater than dose proportional exposure following 1-hour intravenous (IV) infusions over a 3 to 30 mg/kg dose range (Reports DS-2014-055, DS-2014-097, and DS-2015-055). The mean systemic clearance was 7.54, 3.05, 2.38, and 1.24 mL/h/kg at 3, 10, 20, and 30 mg/kg, respectively. The mean volume of distribution during the terminal disposition phase after IV administration ranged between 57 and 70 mL/kg in all dose groups, suggesting that modakafusp alfa is confined to a large extent to the circulatory system. The estimated mean $t_{1/2}$ (half-life) value ranged from 9.97 to 33.8 hours over the 3 to 30 mg/kg dose range. There were no noteworthy sex-related differences in toxicokinetic parameter values.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

4.2.3.2 Toxicology Studies

A series of toxicology studies were conducted in the cynomolgus monkey with a 1-hour IV infusion of modakafusp alfa, including a single-dose exploratory study; an exploratory repeat-dose, range-finding study with weekly and twice-weekly (BIW) dosing; a GLP-compliant, once weekly, 29-day repeat-dose study with a 14-day recovery period and safety pharmacology endpoints; and a second 4-week, GLP-compliant, repeat-dose study with once-weekly dosing. Monkeys are the only relevant nonclinical species identified based on the binding of modakafusp alfa to CD38 from various species.

No remarkable toxicity was noted following a single 1-hour IV infusion of modakafusp alfa at dose levels up to 20 mg/kg. Neopterin levels (a biomarker of IFN biological activity) were increased at 24 hours postdose and were still above baseline at up to 240 hours postdose. Slight decreases in leukocytes driven primarily by decreases in lymphocytes, and transient slight increases in liver parameters (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were also observed.

In repeat-dose studies longer than 14 days, in addition to similar findings as described above, ADA-mediated loss of exposure and hypersensitivity reactions were observed that resulted in early mortalities at ≥10 mg/kg. However, these reactions are considered poorly predictive of a human health risk.

Tolerability was also assessed in a pharmacology combination study of modakafusp alfa with lenalidomide (Report H929-e284), pomalidomide (Report H929-e285), and daratumumab (Report H929-e324) in female CB17 SCID mice bearing H929 xenografts. No modakafusp alfa- or combination related mortality, clinical signs, or body weight effects were noted.

4.2.4 Clinical Experience

Clinical studies are ongoing with modakafusp alfa as a single agent in adult patients with relapsed or refractory multiple myeloma (RRMM) (Study TAK-573-1501) and with modakafusp alfa as a single agent and in combination with pembrolizumab in adult patients with advanced or metastatic solid tumors (TAK-573-1001). TAK-573-2001 is a newly opened study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of modakafusp alfa in combination with daratumumab in patients with RRMM.

4.2.4.1 TAK-573-1501

The first-in-human study TAK-573-1501, "A Phase 1/2 Open-label Study to Investigate the Safety and Tolerability, Efficacy, Pharmacokinetics, and Immunogenicity of Modakafusp Alfa as a Single Agent in Patients with Relapsed Refractory Multiple Myeloma," enrolled the first patient on 09 October 2017. As of the data cutoff date of 22 October 2021, 90 subjects have been enrolled into the study.

This study is being conducted in 3 parts: Part 1 is dose escalation, Part 2 is dose expansion, and Part 3 is designed as an extension study to assess safety and efficacy. The phase 1 single agent portion of the study follows a 3 + 3 dose escalation design to determine a maximum tolerated

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

dose (MTD) based on the observation of dose-limiting toxicities (DLTs) or an optimal biologic dose.

Part 1 of Study TAK-573-1501 involved extensive dose escalation with 10 modakafusp alfa dose levels ranging from 0.001 mg/kg to 6.0 mg/kg on 4 different dosing schedules and included a total of 54 patients. The optimal schedule for modakafusp alfa in MM patients was assessed as once every 4 weeks (Q4W) based on the recovery time of hematological toxicities. The MTD at this schedule was established as 3 mg/kg as 6 mg/kg exceeded the MTD with 2 DLTs (NCI Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0 Grade 3 infusion-related reaction [IRR] and prolonged Grade 4 thrombocytopenia and neutropenia, resulting in a greater than 2-week delay in start of Cycle 2). No DLTs were seen at 3 mg/kg. Preliminary efficacy activity was also seen in dose escalation, with 1 partial response (PR) and 2 minimal responses in 5 patients at 1.5 mg/kg on the Q4W schedule and 1 PR and 1 complete response (CR) (patient ongoing at Cycle 21) in 7 patients at 3 mg/kg on the Q4W schedule.

The primary objective of Part 2 of Study TAK-573-1501 (dose expansion) is to provide a preliminary evaluation of the clinical activity of 1 or more schedules of single-agent modakafusp alfa. Additional cohorts in combination with dexamethasone are to be carried out with one or more selected schedules. The aim of this approach is to obtain preliminary information on the effect of standard doses of dexamethasone on modakafusp alfa safety, efficacy, and pharmacodynamic endpoints.

As of the data cutoff of 17 November 2022, 100 patients have been enrolled into Parts 1 and 2 of Study TAK-573-1501, and 22 patients have been enrolled into Part 3 as of 14 December 2022. The optimal schedule for modakafusp alfa was determined to be Q4W based on the recovery time of hematological toxicities, and the MTD is 3 mg/kg, which was exceeded at 6 mg/kg with 2 DLTs (1 event of thrombocytopenia and neutropenia and 1 event of Grade 3 IRR).

In the 1.5 mg/kg treatment group (N = 30), toxicities were primarily hematologic, with thrombocytopenia and neutropenia observed at rates of 73% (17% Grade 4) and 70% (30% Grade 4), respectively. IRRs have been observed at a rate of 30%, with only 2 events (2.2%) Grade ≥3. Toxicities have been managed with dose delays and supportive care and have rarely resulted in study drug discontinuation or dose reduction.

Based on overall study data, 11 of 85 immunogenicity-evaluable patients (13%) tested ADA positive and 4 of the 85 immunogenicity-evaluable patients (5%) tested NAb positive at the beginning of the study before modakafusp alfa treatment (ie, at baseline). After initiation of modakafusp alfa treatment (ie, after treatment), 49 of 85 immunogenicity-evaluable patients (58%) were ADA positive and 36 of 85 immunogenicity-evaluable patients (42%) were NAb positive at least 1 posttreatment visit, with 48% of the immunogenicity-evaluable patients having treatment-induced ADA and 6% having treatment-boosted ADA. The incidence of patients who tested ADA positive post-treatment was similar across the dose groups. The maximum posttreatment titers for ADA-positive patients ranged from 75 to 1,480,000.

In terms of potential impact of immunogenicity outcomes, modakafusp alfa C_{max} tended to be lower in ADA-positive patients than ADA-negative patients. The degree of reduction tended to

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

increase as the study duration increased and the magnitude of immunogenicity increased. The reduction in C_{max} may be partly due to the potential interference of high-tittered ADA in the modakafusp alfa unbound PK assay. The impact of immunogenicity on modakafusp alfa PK remains to be further characterized.

The potential impact of the ADA and NAb on PK, safety, efficacy, and clinical endpoints will be further evaluated in this and future studies.

Integrated dose- and exposure-response relationships based on preliminary pharmacodynamic (eg, serum M-protein and free light chain [FLC]), efficacy, and safety data indicate that 1.5 and 3 mg/kg Q4W dosing are within the optimal biological dose range. The 1.5 mg/kg Q4W dose group (N = 30) demonstrated an objective response rate of 43.3% and a clinical benefit rate (CBR) of 53.3%. Although median duration of response (DOR) has not been reached, 7 patients have had a response >6 months and are being followed up to assess durability and deepening of response. Given the small sample size at the 3 mg/kg dose, the possibility of improved clinical benefit at a dose of 3 mg/kg compared with 1.5 mg/kg cannot be ruled out; therefore, a 2-dose randomization is planned (Part 3) to identify the optimal dose of single-agent modakafusp. Part 3 (extension phase) of Study TAK-573-1501 is designed as a noncomparative 2-arm study (118 patients planned in each arm) that randomizes patients to modakafusp alfa 120 or 240 mg (the fixed-dose equivalents of 1.5 and 3.0 mg/kg, respectively) to assess response rates, DOR, and safety to identify the modakafusp alfa dose with the optimal benefit-risk profile. As of the data cutoff of 14 December 2022, 22 patients have been enrolled in Part 3. The primary endpoint is the confirmed objective response rate assessed by an independent review committee according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Kumar et al. 2016). In addition, the efficacy of modakafusp alfa will be assessed by measuring EFS, progression-free survival (PFS), time to response (TTR), DOR, time to progression (TTP), and overall survival (OS).

4.2.4.2 TAK-573-1001

TAK-573-1001, "An Open-Label, Dose-Escalation Phase 1b/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Antitumor activity of Modakafusp Alfa (TAK-573) as a Single Agent and in Combination with Pembrolizumab in Adult Patients with Advanced or Metastatic Solid Tumors," is an ongoing study in patients with histologically confirmed advanced or metastatic solid tumors. As of the data cutoff of 23 November 2021, 21 patients have been enrolled into modakafusp alfa single-agent treatment cohorts ranging from 0.1 to 1.5 mg/kg once every 3 weeks (Q3W).

As of Protocol Amendment 6 (28 July 2022), the study consists of 2 phases. The phase 1b dose-escalation portion of the study enrolled patients with advanced/metastatic solid tumors to determine the single-agent recommended phase 2 dose (RP2D) and schedule of modakafusp alfa for further testing. Enrollment into the phase 2 expansion portion of the study was initiated once the RP2D of modakafusp alfa was determined in phase 1b of the study. The phase 2 part is assessing modakafusp alfa in combination with pembrolizumab, beginning with a safety-lead in period to evaluate safety and tolerability of the combination during the Cycle 1 DLT evaluation

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

period. Following completion of the safety lead-in phase and review of safety data, the combination cohorts are enrolling patients with unresectable/metastatic melanoma in 3 subgroups: patients with primary resistance to no more than 2 prior lines of treatments containing anti–programmed cell death protein 1 (PD-1) in the metastatic setting, patients with acquired resistance to no more than 2 prior lines of anti-PD1–containing treatments in the metastatic setting, and patients naïve to prior line of anti-PD1–containing treatments in the metastatic setting.

As of the data cutoff of 23 October 2022, a total of 28 patients have been enrolled in the study: 21 in the phase 1b dose escalation, 3 in the phase 2 safety lead-in, and 4 in the phase 2 expansion portion. The phase 1b dose-escalation portion treated patients with single-agent modakafusp alfa doses ranging from 0.1 to 1.5 mg/kg Q3W. A total of 2 DLTs were identified across all dose levels, both occurring at the 1.5 mg/kg dose: Grade 4 thrombocytopenia and Grade 3 confusion (n = 1 each). The MTD was determined to be 1.5 mg/kg Q3W based on protocol-defined MTD declaration rules following a Bayesian Logistic Regression Model. The RP2D was determined to be 1.0 mg/kg Q3W, and the PAD range was determined to be 0.1 to 1.5 mg/kg Q3W.

Based on the available data as of August 2022, 1 of 19 (12%) and 19 of 19 (100%) of the immunogenicity-evaluable patients (ie, patients with ADA evaluated at baseline and at least 1 posttreatment visit) with solid tumors had positive ADA assays at baseline and after treatment, respectively. No dose response on the ADA incidence and titer was observed. The first incidence of posttreatment ADA was reported as early as Cycle 2 Day 1 (earliest posttreatment sampling), and both transient and persistent ADA were observed. The ADA titer ranged from 75 to 1,480,000.

The potential impact of the ADA and NAb on PK, pharmacodynamics, safety, efficacy will be further evaluated in this and future studies.

4.2.4.3 TAK-573-2001

TAK-573-2001, "A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination with Daratumumab SC in Patients With Relapsed or Refractory Multiple Myeloma" is a newly opened study in patients with RRMM. The first part of the study is designed to assess the safety and tolerability of modakafusp alfa and daratumumab administered subcutaneously (SC). The data from TAK-573-2001 will guide the TAK-573-1502 dose escalation/de-escalation phase of multiple triplet combination arms.

4.2.4.4 TAK-573-1502 Arm 4

As of 27 April 2023, 3 patients had been enrolled in the Arm 4 (modakafusp alfa 80 mg on Day 1 and carfilzomib 20/70 mg/m^2). This cohort was stopped and closed due to SAEs in the first 3 patients treated. These events consisted of 2 cases of thrombotic microangiopathy (TMA) resulting in hemolytic uremic syndrome and 1 case of acute myocardial infarction. TMA is a known risk with carfilzomib; however, with 2 of 3 initial patients experiencing TMA, a potential

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

synergistic interaction between carfilzomib and modakafusp alfa resulting in an increased incidence of TMA cannot be excluded. These cases are described in the IB.

4.3 Combination Agents

4.3.1 Lenalidomide

Lenalidomide is an analog of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of lenalidomide are mediated through its target, cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including MM (Revlimid (lenalidomide) 2021).

Lenalidomide has been indicated for the treatment of adult patients with MM in combination with dexamethasone since 2006. It was also approved as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT).

4.3.2 Pomalidomide

Pomalidomide is a thalidomide analog with immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of pomalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. Pomalidomide inhibited the proliferation of lenalidomide-resistant MM cell lines. Pomalidomide enhanced T-cell– and NK cell–mediated immunity and inhibited production of proinflammatory cytokines by monocytes (Pomalyst (pomalidomide) Capsules 2020).

Pomalidomide was approved in combination with dexamethasone for patients with MM who have received at least 2 prior therapies, including lenalidomide and a PI, and had demonstrated disease progression on or within 60 days of completion of the last therapy.

In patients with RRMM, pomalidomide is indicated in combination with daratumumab/dexamethasone in patients who have received at least 1 prior line of therapy including lenalidomide and a PI (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021). Pomalidomide is also used as part of different regimens in combination with bortezomib/dexamethasone, carfilzomib/dexamethasone, daratumumab/dexamethasone, or ixazomib/dexamethasone in RRMM patients (Moreau et al. 2021).

4.3.3 Bortezomib

Bortezomib is a boronic acid PI which is cytotoxic to a variety of cancer cell types in vitro. Bortezomib delays tumor growth in vivo in nonclinical tumor models, including MM. Bortezomib is indicated for treatment of adult patients with MM (Velcade (bortezomib) for Injection 2019). In previously untreated MM patients, bortezomib is approved in combination with melphalan/prednisone (VMP) (Velcade (bortezomib) for Injection 2019). Bortezomib is indicated for the treatment of adult patients with MM in combination with daratumumab/melphalan/prednisone (ie, DVMP) in patients with newly diagnosed multiple

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

myeloma (NDMM) who are ineligible for autologous stem cell transplantation (ASCT) and in combination with daratumumab/thalidomide/dexamethasone (DVTd) in NDMM patients who are eligible for ASCT (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021). In patients with RRMM, bortezomib is indicated in combination with daratumumab and dexamethasone (DVd) (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021), or with selinexor/dexamethasone (SVd) (Xpovio (selinexor) tablets for oral use 2021). Bortezomib is also used in patients with RRMM as part of several different regimens in combination with pomalidomide/dexamethasone (PVd), thalidomide/dexamethasone, cyclophosphamide/dexamethasone (VCd), melphalan/prednisone (VMP), or with dexamethasone (Vd) (Moreau et al. 2021).

4.3.4 Daratumumab and Hyaluronidase-fihj

Daratumumab is an IgG1κ human mAb that binds to CD38 antigens and inhibits the growth of CD38expressing tumor cells by inducing apoptosis directly through Fc (fragment crystallizable) mediated cross-linking as well as by immune-mediated tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.

Daratumumab and hyaluronidase-fihj is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, which is an englycosidase that is approved as a monotherapy and in combination with standard antimyeloma therapies for patients with MM (Darzalex (daratumumab) injection for intravenous use 2021).

4.4 Rationale for the Proposed Study

4.4.1 Modakafusp Alfa

The use of combination strategies is a mainstay of myeloma treatment. Partnering with agents such as PIs and IMiDs for additive or synergistic effects by combining different mechanisms of action allows the targeting of multiple pathways in 1 regimen.

Despite recent advances in the MM field, including the approval of immune-based therapies beyond mAbs such as antibody-drug conjugates and chimeric antigen receptor T-cell therapies (eg, idecabtagene vicleucel and ciltacabtagene autoleucel) (Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021), long-term disease control is not assured and cure remains elusive. As the vast majority of patients will require ongoing therapies, there is still a need for novel therapies and regimens, especially those that introduce a unique mechanism of action.

Modakafusp alfa displayed robust antitumor activity in combination with standard-of-care (SOC) agents in mouse models of MM. Cotreatment with a suboptimal dose of modakafusp alfa improved the antitumor activity of IMiDs (lenalidomide, pomalidomide), PIs (bortezomib, ixazomib), melphalan, and cyclophosphamide (Reports H929-e284 and TPA-38-053).

Clinical studies are ongoing with modakafusp alfa as a single agent in adult patients with RRMM (TAK-573-1501) and with modakafusp alfa in combination with pembrolizumab in adult patients

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

with advanced or metastatic solid tumors (TAK-573-1001) (Section 4.2.4). Single-agent activity was confirmed in patients with RRMM. The main Grade 3/4 toxicities observed were hematologic (Vogl et al. 2021).

The rationale for associating modakafusp alfa with the proposed combination agents in patients with MM in maintenance therapy and in patients with RRMM is based on the single-agent activity observed in the TAK-573-1501 study and preclinical combinatorial activity observed with lenalidomide, pomalidomide, bortezomib, and carfilzomib. Based on the known toxicity profiles of each of these agents, overlapping toxicities are predicted, but they are anticipated to be manageable. Therefore, the objective of this phase 1b study is to determine the safety and tolerability of modakafusp alfa as part of combination therapy in adult patients with MM.

4.4.1.1 Rationale for Modakafusp Alfa Dose

Modakafusp alfa has been characterized in nonclinical studies (see the IB for current information). Two clinical studies, TAK-573-1501 in MM and TAK 573-1001 in solid tumors, are ongoing (Section 4.2.4), and Study TAK-573-2001 has begun enrollment.

The proposed starting dose for modakafusp alfa in all arms of Study TAK-573-1502 is 80 mg Q4W, which is N-1 or N-2 of the potential modakafusp alfa single-agent doses of 120 or 240 mg Q4W, respectively, which are currently being assessed in Part 3 of Study TAK573-1501 for selection of an optimal single-agent dose.

With the modakafusp alfa 80 mg Q4W dose regimen, the median single-dose AUC is expected to be approximately 3 and 6-fold below the potential single agent dose of 120 or 240 mg Q4W, respectively.

Based on the single-agent safety profile of modakafusp alfa from Study TAK-573-1501, the major potential overlapping toxicities anticipated in this study are thrombocytopenia and neutropenia, with the possible clinical manifestations of bleeding and infection. As such, these clinical events were analyzed in patients treated with modakafusp alfa (Study TAK-573-1501) at body weight-based Q3W and Q4W dosing schedules equivalent to flat doses of 70 to 90 mg.

Thrombocytopenia may increase the risk of bleeding. Therefore, in patients treated with modakafusp alfa and concurrent anticoagulation, platelet counts should be carefully monitored and antithrombotic/anticoagulant therapy managed accordingly in an effort to balance the risk of bleeding versus the risk of a venous thromboembolic event or stroke.

Intensive safety monitoring, including rigorous chemistry and hematologic assessments, is included in the initial cycles of the current study. This will enable close monitoring of TEAEs for prompt medical interventions, if needed.

4.4.2 Combination Agents

4.4.2.1 Lenalidomide

Thalidomide is a known human teratogen that causes life-threatening birth defects or embryo-fetal death and is available only under a restricted program. Treatment of patients with

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

MM with PD-1 or programmed cell death ligand 1 (PD-L1) blocking antibody in combination with a thalidomide analog plus dexamethasone is not recommended outside of controlled clinical studies. Lenalidomide (Revlimid), a thalidomide analog, is indicated for the treatment of adult patients with MM in combination with dexamethasone. It was also approved as maintenance therapy following auto-HSCT. The recommended starting dose in maintenance therapy following auto-HSCT is 10 mg once daily (QD) continuously on Days 1 to 28 of repeated 28-day cycles. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg QD if tolerated (Revlimid (lenalidomide) 2021).

Four randomized phase 3 studies have evaluated lenalidomide in maintenance therapy following auto-HSCT. In 2 trials (CALGB 100104, 460 patients and IFM 2005-02, 614 patients), the maintenance dose was 10 mg QD and could be increased to 15 mg QD after 3 months. The dose was increased to 15 mg in 135 patients (58 %) in the CALGB trial and 185 patients (60%) in the IFM trial (Revlimid (lenalidomide) 2021). The CALGB trial reported median TTP and OS of 57 and 114 months, respectively, in the lenalidomide arm versus 29 and 84 months, respectively, compared with placebo (Holstein et al. 2017). Similar results were shown in the IFM study (median PFS 41 months in the lenalidomide group versus 23 months in the placebo group). Two other trials (RV-MM-209, 402 patients and Myeloma XI, 1247 patients) evaluated another dosing schedules at 10 mg, 21 out of 28 days, with no increase of the dose. The RV-MM-209 study reported median PFS and 3-year OS of 42 months and 88%, respectively, in the maintenance arm versus 22 months and 79% in the placebo arm. The Myeloma XI study revealed median PFS and 3-year OS of 57 months and 88% in the lenalidomide group versus 30 months and 80% in the control group.

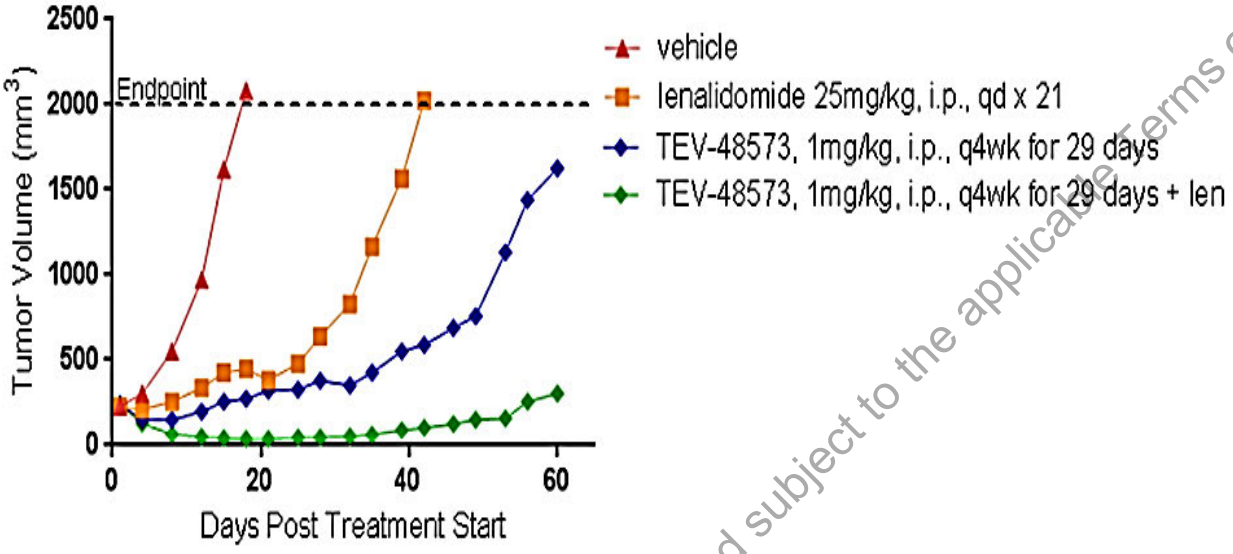
Most common adverse reactions (more than 20% in the lenalidomide arm) across both CALGB and IFM studies included neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhea, rash, fatigue, asthenia, muscle spasm and pyrexia (Revlimid (lenalidomide) 2021).

Lenalidomide maintenance therapy after ASCT is the current SOC in many regions. Several randomized phase 3 studies and meta-analysis reported significant PFS and OS benefits for lenalidomide compared with observation/placebo. However, patients will experience relapse and require new therapy. There is a need to develop new strategies to improve upon lenalidomide maintenance.

As outlined in Figure 4.a and Figure 4.b, lenalidomide combined with modakafusp alfa demonstrated a significant reduction of the median tumor volume in both the NCI-H929 and OPM2 xenograft models.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Figure 4.a Therapeutic Synergy of Modakafusp Alfa Combined With Lenalidomide (Revlimid) in NCI-H929 Mouse Xenograft Model



Source: H929-e284 report.

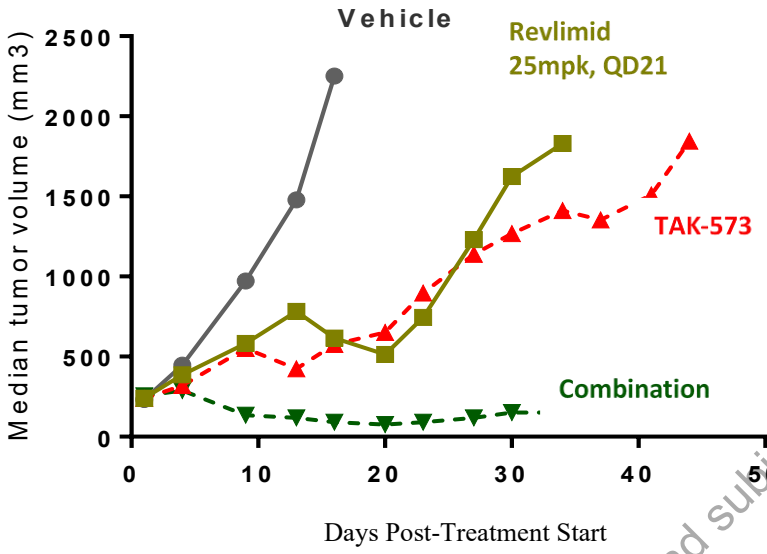
i.p.: intraperitoneal; len: lenalidomide; qd: once daily; q4wk: once every 4 weeks; TEV-48573: modakafusp alfa (TAK-573).

Mice bearing subcutaneous NCI-H929 tumors (170-350 mm^3) were randomized and treated with vehicle, lenalidomide, modakafusp alfa, or a combination of lenalidomide + modakafusp alfa.

Graph shows median tumor volume per group.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Figure 4.b Therapeutic Synergy of Modakafusp Alfa Combined With Lenalidomide (Revlimid) in OPM2 Mouse Xenograft Model



Source: H929-e284 report.

mpk: mg/kg; QD21: every day for 21 days; TAK-573: modakafusp alfa.

Mice bearing subcutaneous OPM2 tumors (average starting volume ~150 mm^3) were randomized and treated with vehicle, lenalidomide, modakafusp alfa, or a combination of lenalidomide + modakafusp alfa.
Graph shows median tumor volume per group.

4.4.2.2 Pomalidomide

Pomalidomide was approved in combination with dexamethasone for patients with MM who have received at least 2 prior therapies, including lenalidomide and a PI, and had demonstrated disease progression on or within 60 days of completion of the last therapy. Pomalidomide is supplied in 1, 2, 3, and 4 mg capsules. The recommended dosage is 4 mg per day taken orally (PO) on Days 1 through 21 of repeated 28-day cycles until disease progression; reduced doses are recommended for patients with hepatic impairment.

In a trial of 221 patients with relapsed MM who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib, patients were randomized to pomalidomide alone or pomalidomide with low-dose dexamethasone. The overall response rate (ORR) by an independent review committee using EBMT (European Blood and Marrow Transplantation) criteria was 7.4% in the pomalidomide alone and 29.2% in the combination arm. A second trial comparing these treatment regimens in 455 patients with RRMM reported median PFS and ORR of 3.6 months and 23.5%, respectively, in the combination arm versus 1.8 months and 3.9%, respectively, with pomalidomide alone (Pomalyst (pomalidomide) Capsules 2020).

Thalidomide is a known human teratogen that causes severe life-threatening birth defects. Pomalidomide is a thalidomide analog and is available only under a restricted program. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

thalidomide analog plus dexamethasone is not recommended. Coadministration of strong cytochrome P450 (CYP)1A2 inhibitors (eg, ciprofloxacin and fluvoxamine) should be avoided.

Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia (Pomalyst (pomalidomide) Capsules 2020).

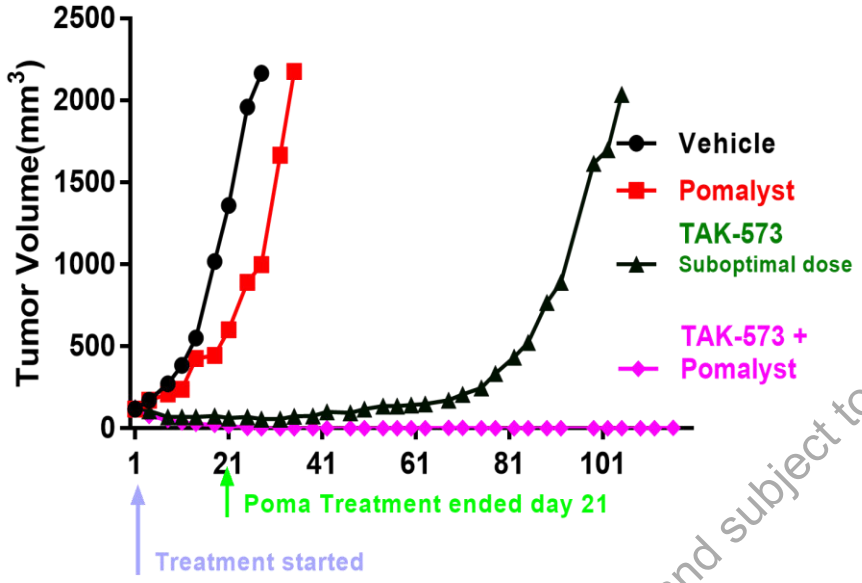
Pomalidomide in combination with bortezomib and dexamethasone was evaluated and compared with bortezomib plus dexamethasone in patients with RRMM (OPTIMISMM trial). Pomalidomide was also combined with carfilzomib and dexamethasone (EMN011/HO114 trial). (Moreau et al. 2021). In the EQUULEUS trial, pomalidomide in combination with daratumumab and dexamethasone was evaluated in patients with MM who had received a prior PI and an IMiD (see Section 4.4.2.4).

Lower dosing regimens of pomalidomide were evaluated. Lacy et al have shown that pomalidomide 2 mg daily with weekly dexamethasone demonstrated impressive activity in RRMM: 63% of the patients had a confirmed response (Lacy et al. 2009). Later, Lacy et al also reported 2 sequential phase 2 trials comparing pomalidomide 2 versus 4 mg daily (on Days 1-28 of a 28-day cycle) with weekly low-dose dexamethasone in patients with MM refractory to both lenalidomide and bortezomib. Results showed no advantage for 4 mg over the 2 mg daily dosing of pomalidomide (Lacy et al. 2011).

Modakafusp alfa in combination with pomalidomide was evaluated in the NCI-H929 xenograft tumor model. Mice bearing NCI-H929 SC tumors (average starting tumor volume = 150 mm^3) were randomized and treated with vehicle (200 µL, IP, BIW × 3), pomalidomide (2.5 mg/kg, QD × 21), modakafusp alfa (2 mg/kg, BIW × 4, IP) or pomalidomide + modakafusp alfa. Individual tumor volumes were measured BIW. Figure 4.c shows median tumor volume per treatment arm BIW × 4 QD × 21. Pomalidomide combination with modakafusp alfa demonstrated a significant reduction of the median tumor volume in the NCI-H929 xenograft models (Figure 4.c).

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Figure 4.c Activity of Modakafusp Alfa Combined With the IMiD Pomalidomide (Pomalyst) in NCI-H929 MM Xenograft Tumor Model



Source: H929-e285 report.
IMiD: immunomodulatory drug; MM: multiple myeloma; TAK-573: modakafusp alfa.
Pomalidomide treatment ended at Day 21.

4.4.2.3 Bortezomib

Bortezomib (Velcade) is a PI indicated for treatment of adult patients with MM. The recommended dosage is 1.3 mg/m^2 BID on Days 1, 4, 8, and 11, followed by a 10-day rest period from Days 12 to 21. After 8 cycles, patients can follow a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) (Velcade (bortezomib) for Injection 2019).

An integrated safety analysis of 1008 patients who received single-agent bortezomib at the above dosage demonstrated that >20% of patients had adverse events (AEs) of nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%); 11% of patients experienced at least 1 Grade ≥4 toxicity, and 22% of patients discontinued due to AEs (Velcade (bortezomib) for Injection 2019).

Bortezomib in combination with pomalidomide plus dexamethasone was evaluated in patients with RRMM (see Section 4.4.2.2).

DVd was evaluated in the CASTOR trial. ORR was 79.3% in the DVd group and 59.9% in the Vd group. In responders, the median TTR was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. Serious adverse reactions (SARs) occurred in 42% of patients in the DVd arm compared with 34% in the Vd arm. SARs with at least a 2% greater incidence in the DVd arm compared with the Vd arm were upper

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each) (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

Bortezomib weekly schedule was evaluated in several trials. In the BOSTON trial, once weekly bortezomib in combination with Selinexor was compared with BIW bortezomib plus dexamethasone. In the SVd group, bortezomib was administered once per week SC on Days 1, 8, 15, and 22 of a 5-week cycle. In the Vd group, bortezomib was administered SC in accordance with the approved regimen of 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 3-week cycle (Grosicki et al. 2020). In the RVD-lite regimen (Revlimid, Velcade, dexamethasone), bortezomib 1.3 mg/m^2 was administered weekly SC on Days 1, 8, 15 and 22 of a 35-day cycle (O'Donnell et al. 2018). In a retrospective study, Cook et al. evaluated the response rates and outcomes with different schedules of bortezomib in the induction therapy VRd (bortezomib/lenalidomide/ dexamethasone) administered in patients with NDMM. Bortezomib was administered BIW every 21 days in 43%, once weekly every 21 days in 41%, and once weekly every 28 days in 16% of patients. With a median follow-up time of 37 months, no difference in PFS or OS among the groups was found (Cook et al. 2021).

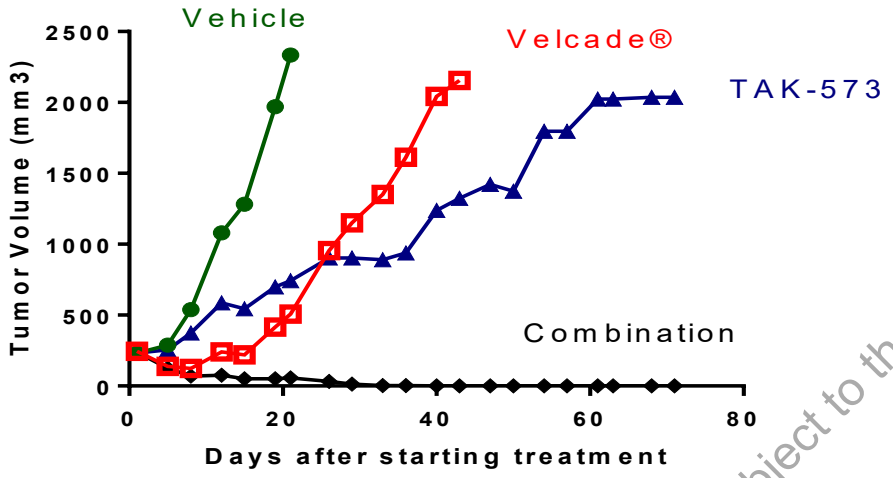
Combination therapy with bortezomib and IFN-α was explored in melanoma. In their preclinical study, Lesinski et al demonstrated that IFN-α in combination with bortezomib induced synergetic apoptosis in human melanoma cell lines, prolonged survival in a murine model of melanoma, and significantly reduced tumor growth in a xenograft model of human melanoma in athymic mice compared with either agent alone (Lesinski et al. 2008).

This combination therapy was evaluated in a phase 1 study (16 patients) and was well tolerated overall; toxicities were similar to those with bortezomib and/or IFN-α treatment alone. Common Grade 3 toxicities included fatigue, vomiting, and diarrhea. Grade 4 toxicities were fatigue and lymphopenia (Markowitz et al. 2014).

As shown in Figure 4.d and Figure 4.e, bortezomib combined with modakafusp alfa demonstrated a significant reduction of the median tumor volume in both the NCI-H929 and OPM2 xenograft models.

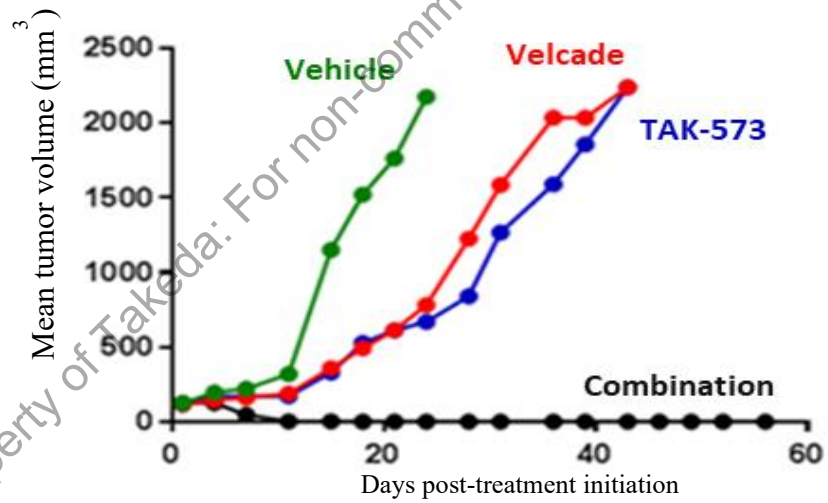
Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Figure 4.d Activity of Modakafusp Alfa Combined With the Proteasome Inhibitor Bortezomib (Velcade) in NCI-H929 MM Xenograft Tumor Model



Source: TPA-38-053 report.
BIW: twice weekly; IP: intraperitoneal(ly); MM: multiple myeloma; QD: once daily. TAK-573: modakafusp alfa.
Mice bearing subcutaneous NCI-H929 tumors (average starting tumor volume = 250 mm^3) were randomized and treated with vehicle (200 µL, IP, BIW × 3), bortezomib (1 mg/kg, BIW × 4), modakafusp alfa (2.5 mg/kg, BIW × 3, IP) or bortezomib + modakafusp alfa.
Individual tumor volumes were measured BIW. Graph shows median tumor volume per treatment arm.

Figure 4.e Therapeutic Synergy of Modakafusp Alfa Combined With the Proteasome Inhibitor Bortezomib (Velcade) in OPM2 Mouse Xenograft Model



Source: TPA-38-053 report
TAK-573: modakafusp alfa.
Mice bearing subcutaneous OPM2 tumors (average starting volume ~150 mm3) were randomized and treated with vehicle, bortezomib (Velcade), modakafusp alfa, or a combination of bortezomib (Velcade) + modakafusp alfa.
Graph shows median tumor volume per group.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

4.4.2.4 Daratumumab

Daratumumab is an IgG1κ human mAb that binds to CD38 antigens and inhibits the growth of CD38-expressing tumor cells.

Daratumumab monotherapy was evaluated in patients with RRMM who had received at least 3 prior lines of therapy, including a PI and an immunomodulatory agent, or who were double-refractory to a PI and an immunomodulatory agent (SIRIUS trial, 106 patients) with RRMM in 3 open-label, clinical trials. The ORR was 29.2% with stringent CR (sCR) of 2.8%. The median DOR was 7.4 months (range: 1.2 to 13.1+ months). Study GEN501 was an open-label dose escalation trial evaluating daratumumab monotherapy in patients with RRMM who had received at least 2 different cytoreductive therapies (42 patients). ORR was 36% (95% CI: 21.6, 52.0%) with 1 CR and 3 very good partial responses (VGPRs).

The safety of daratumumab was evaluated in 156 adult patients with RRMM in 3 open-label, clinical trials. The most frequent SARs were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections.

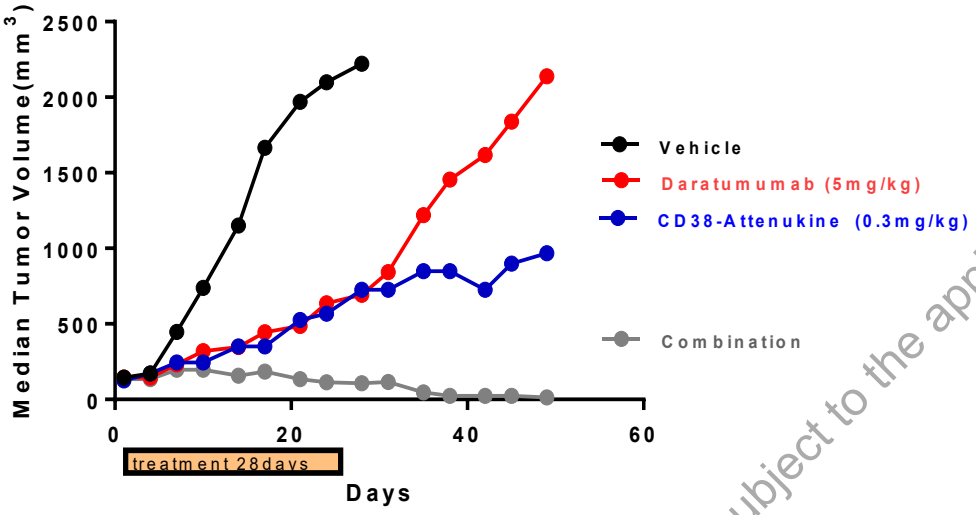
EQUULEUS was an open-label, multicohort trial that evaluated the combination of daratumumab with once-weekly carfilzomib (20/70 mg/m^2) and dexamethasone in patients with RRMM who had received at least 1 to 3 prior lines of therapy. The ORR was 81% with sCR of 21% and CR of 14%. The median DOR was 28 months (95% CI: 20.5, not estimable). SARs were reported in 48% of patients. The most frequent SARs reported were pneumonia (4.7%), upper respiratory tract infection (4.7%), basal cell carcinoma (4.7%), influenza (3.5%), general physical health deterioration (3.5%), and hypercalcemia (3.5%). IRRs on the day of administration of any daratumumab dose or on the next day occurred in 44% of patients.

Daratumumab in combination with pomalidomide and dexamethasone was also evaluated in the EQUULEUS trial, in which 103 patients with MM who had received a prior PI and an immunomodulatory agent received 16 mg/kg daratumumab in combination with pomalidomide and low-dose dexamethasone until disease progression. The ORR was 59.2% with sCR of 7.8% and CR of 5.8%. The median DOR was 13.6 months (range: 0.9+ to 14.6+ months). The overall incidence of SARs was 49%. SARs reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021). Daratumumab was also evaluated in combination with bortezomib and dexamethasone (see Section 4.3.3).

Daratumumab in combination with modakafusp alfa was evaluated in the NCI-H929 xenograft model. As shown in Figure 4.f, daratumumab combined with modakafusp alfa demonstrated a significant reduction of the median tumor volume in the NCI-H929 xenograft models.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Figure 4.f Activity of Modakafusp Alfa Combined With the Anti-CD38 Antibody Daratumumab in NCI-H929 MM Xenograft Tumor Model



Source: H929-e284 report.

BIW: twice weekly; IP: intraperitoneal(ly).

Mice bearing subcutaneous NCI-H929 tumors (average starting tumor volume = 250 mm^3) were randomized and treated with vehicle (200 µL, IP, BIW × 3), daratumumab (5 mg/kg, BIW × 4), CD38-attenukine (modakafusp alfa 0.3 mg/kg, BIW × 4, IP) or daratumumab + modakafusp alfa.

Individual tumor volumes were measured BIW. Graph shows median tumor volume per treatment arm.

4.5 Risks and Benefits

4.5.1 Benefit-Risk Profile of Modakafusp Alfa

Modakafusp alfa has been administered to a limited number of patients with MM and solid tumors in ongoing studies.

In Study TAK-573-1501, initial efficacy with modakafusp alfa was observed on Schedule A at a dose of 0.1 mg/kg, with 1 patient having a PR at Cycle 2 and remaining in PR until Cycle 14. Two additional responses were observed in patients treated at 0.4 mg/kg. Of the 12 patients receiving modakafusp alfa 0.75 mg/kg (3 patients per Schedule A, 3 patients per Q3W, and 6 patients Q4W), 1 patient treated on the Q3W schedule had a minimal response for 2 cycles. Thus, of the 52 patients treated at doses less than 1.5 mg/kg (41 patients in escalation cohorts at 4 schedules and 11 patients in expansion cohorts at a dose of 0.4 mg/kg Q3W), responses were observed in only 2 patients.

As of the data cutoff of 17 November 2022, a total of 30 patients were enrolled in the expansion and escalation parts at the dose of 1.5 mg/kg Q4W. The objective response rate in these patients was 43.3%, and the CBR was 53.3%. In 22 triple-refractory and penta-exposed patients, the objective response rate was 40.9%.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

4.5.1.1 Nonclinical Safety Summary

Based on nonclinical studies in cynomolgus macaques, the adverse drug reactions that may be associated with modakafusp alfa administration are decreases in blood cell counts and elevations in liver enzymes. Other findings from repeat-dose general toxicity studies were thought to result from ADA-mediated hypersensitivity reactions, which are considered poorly predictive of responses in humans. Additional information regarding benefits and risks to patients can be found in the IB.

There were no direct modakafusp alfa-induced changes in CNS, respiratory, and cardiovascular parameters evaluated on general toxicity studies in cynomolgus monkeys.

In MM mouse pharmacology models, no effects on mortality, body weight, or clinical signs were noted following the administration of modakafusp alfa with combination agents including lenalidomide (H929-e284), pomalidomide (H929-e285) or daratumumab (H929-e324). Combination toxicity studies have not been performed.

4.5.1.2 Clinical Safety Summary

Please see the current IB for details of modakafusp alfa clinical safety.

Hematologic Toxicities

The predominant toxicities of modakafusp have been hematologic, and these effects have been managed with supportive care and dose delays.

In Study TAK-573-1501, the most common TEAEs were hematologic, including thrombocytopenia (including platelet count decreased), followed by neutropenia (including neutrophil count decreased), leukopenia, anaemia, and lymphocyte count decreased.

IRRs

Patients receiving modakafusp alfa have experienced IRRs. No patients have experienced anaphylactic shock. Reactions such as pyrexia, chills, nausea, vomiting, flushing, dyspnea, cough, headache, dizziness, rash, pruritus, hypoxia, hypertension, tachycardia, blurred vision, abdominal pain, and back pain were observed. In modakafusp alfa studies, IRRs are designated as adverse events of special interest (AESIs).

It is important to monitor for signs and symptoms of hypersensitivity reactions and treat the patient accordingly. Resuscitation medications and equipment should be available before, during, and after the infusion. Premedications and treatment should be provided as described in Section 8.1.1.1.

Neuropsychiatric AEs

Neuropsychiatric AEs have been reported in modakafusp alfa clinical trials.

Liver Function

Patients receiving modakafusp alfa have experienced elevation in liver enzymes.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Cytokine Release Syndrome

Modakafusp alfa elicited a low level of cytokine release (TNF-α, IL-6, IL-8, IFN-γ, and IL-2) from human PBMCs in vitro, less than or comparable to that observed with palivizumab, and is therefore unlikely to induce cytokine release syndrome (CRS) in the clinic. However, CRS is a potential outcome of treatment with therapeutic protein products and patients should be monitored for this potential event.

Interference With Serologic Testing

Modakafusp alfa has been shown to interfere with serological testing due to binding to CD38 on red blood cells (RBCs), which results in positive direct and indirect antiglobulin tests. The duration of modakafusp alfa–mediated positive direct and indirect antiglobulin tests has not yet been evaluated. The determination of a patient's ABO and Rh blood type are not affected by the presence of modakafusp alfa. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received modakafusp alfa. Type and screen patients before starting modakafusp alfa if this was not performed previously.

For more detailed information on the AEs associated with modakafusp alfa, as well as the identified and potential risks, please refer to the most recent IB.

Clinical safety will be monitored per the assessments described in the schedules of events (SOEs). Dose modification should be applied per the guidelines in Section 8.6.

4.5.2 Benefit-Risk Profile of the Combination Agents

Benefits of the combination agents are described in Section 4.3.

Adverse Effects of Lenalidomide

The most common adverse reactions occurring in at least 20% of patients treated with lenalidomide in MM trials were diarrhea, fatigue, anemia, constipation, neutropenia, leukopenia, peripheral edema, insomnia, muscle cramp/spasms, abdominal pain, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, bronchitis, nasopharyngitis, gastroenteritis, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor.

Lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis and pulmonary embolism as well as risk of myocardial infarction and stroke in patients with MM who were treated with lenalidomide and dexamethasone therapy. Refer to the lenalidomide prescribing information for more details (Revlimid (lenalidomide) 2021).

Adverse Effects of Pomalidomide

In patients with MM treated with pomalidomide, the most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, upper respiratory tract infection, back pain, and pyrexia. Neutropenia was the most frequently reported Grade 3/4 AE. Refer to the pomalidomide prescribing information for more details (Pomalyst (pomalidomide) Capsules 2020).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Adverse Effects of Bortezomib

Most commonly reported adverse reactions (≥20%) in clinical studies of bortezomib in patients with MM include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia and anorexia. Refer to the bortezomib prescribing information for more details (Velcade (bortezomib) for Injection 2019).

Adverse Effects of Daratumumab and Hyaluronidase-fihj

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, anemia, leukopenia, and lymphocytopenia. Refer to daratumumab and hyaluronidase-fihj prescribing information for more details (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

Systemic administration-related reactions occurred in 9% of patients (Grade 2: 3.2%, Grade 3: 1%). Eight percent of patients experienced systemic administration-related reactions with the first injection, 0.3% with the second injection. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days).

Daratumumab binds to CD38 on RBCs and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's blood group and Rh are not impacted (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives of the study are:

Group 1: MM Maintenance

- To determine the safety and tolerability of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with MM after ASCT.
- To determine the RP2D of the combination therapy with modakafusp alfa.

Group 2 and Group 3: RRMM Doublets and Triplets

- To determine the safety and tolerability of modakafusp alfa as part of either a 2- or 3-drug combination therapy in adult patients with RRMM.
- To determine the RP2D of the combination therapy with modakafusp alfa (recommended doses of the doublet or triplet combinations).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

5.1.2 Secondary Objectives

The secondary objectives of the study are:

Group 1: MM Maintenance

- To evaluate the preliminary efficacy of modakafusp alfa and lenalidomide combination therapy as maintenance in adult patients with MM after ASCT.
- To evaluate the rate and duration of minimal/measurable residual disease (MRD) negativity (MRD[-]).
- To collect PK data to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

Group 2 and Group 3: RRMM Doublets and Triplets

- To evaluate the preliminary efficacy of modakafusp alfa as part of either a 2- or 3-drug combination therapy in adult patients with RRMM.
- To evaluate the rate and duration of MRD[-].
- To collect PK data for modakafusp alfa to support population PK and exposure-response analysis of modakafusp alfa when given in combination therapy.
- To characterize the immunogenicity profile of modakafusp alfa when given in combination therapy.

5.1.3 [redacted]

[redacted]

5.2 Estimands

Not applicable.

5.3 Endpoints

5.3.1 Primary Endpoints

The primary endpoints of the study for Groups 1, 2, and 3 (MM maintenance, RRMM doublets, and RRMM triplets) are:

- Occurrence of DLTs in Cycle 1.
- Frequency and severity of TEAEs.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

5.3.2 Secondary Endpoints

Secondary endpoints are:

Group 1: MM Maintenance

- PFS.
- ORR (per investigator assessment).
- DOR.
- Rate of MRD[-] at a threshold of 10^{-5} in patients at 6 months, 1 year, and 2 years after the start of treatment.
- Duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-].
- ADA incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).

Group 2 and Group 3: RRMM Doublets and Triplets

- OS.
- ORR.
- PFS.
- TTP.
- Time to next treatment (TTNT).
- DOR.
- Disease control rate (DCR).
- EFS.
- TTR.
- Rate of MRD[-] CR at a threshold of 10^{-5} with CR assessed by the investigator.
- Rate of MRD[-] at a threshold of 10^{-5}.
- Duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-].
- ADA incidence and characteristics (eg, titer and specificity) and NAb.

5.3.3 [redacted]

[redacted]

[redacted]

[redacted]

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a global multicenter, open-label, phase 1b study designed to evaluate the safety and tolerability of modakafusp alfa in combination therapy and determine the RP2D of the combination therapy with modakafusp alfa in adult patients with MM. The study will be conducted using 3 groups based on MM status; the combinations to be evaluated within each group are as follows.

Group 1: MM Maintenance

Arm 1: Modakafusp alfa + lenalidomide after ASCT as maintenance therapy in MM

Group 2: RRMM Doublets

Arm 2: Modakafusp alfa + pomalidomide (MP) in RRMM

Arm 3: Modakafusp alfa + bortezomib (MV) in RRMM

Arm 4: Modakafusp alfa + carfilzomib (MK) in RRMM (*closed to enrollment*)

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

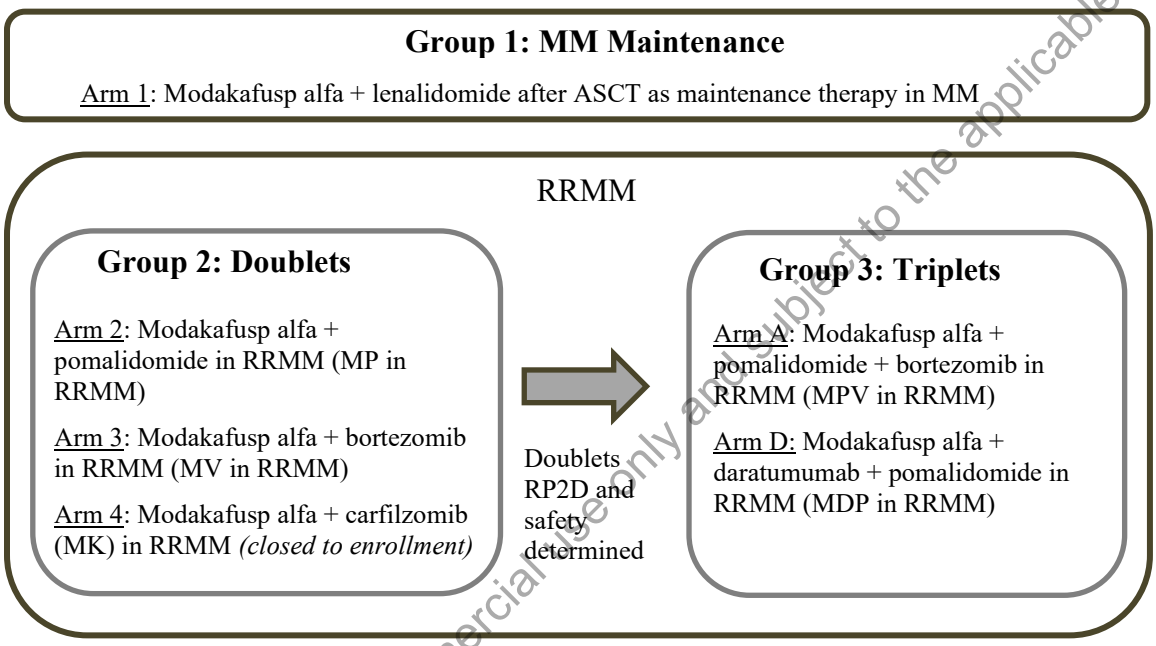
Group 3: RRMM Triplets

Arm A: Modakafusp alfa + pomalidomide + bortezomib (MPV) in RRMM

Arm D: Modakafusp alfa + daratumumab + pomalidomide (MDP) in RRMM

The overall study schema is shown in Figure 6.a.

Figure 6.a Schematic of Study Design



ASCT: autologous stem cell transplantation; MDP: modakafusp alfa, daratumumab, and pomalidomide; MK: modakafusp alfa and carfilzomib (Kyprolis); MM: multiple myeloma; MP: modakafusp alfa and pomalidomide; MPV: modakafusp alfa, pomalidomide, and bortezomib (Velcade); MV: modakafusp alfa and bortezomib (Velcade); RP2D: recommended phase 2 dose; RRMM: relapsed/refractory multiple myeloma.

➔ After the doublet RP2D is determined in Group 2 RRMM doublet combinations, dose escalation of modakafusp alfa in Group 3 RRMM triplet combinations will begin.

Patient participation will include a screening phase, a treatment phase, and a follow-up phase. The screening phase will be up to approximately 21 days before Cycle 1 Day 1.

Patients will be evaluated approximately 30 days after the last dose of treatment (end-of-treatment [EOT] visit) or before the start of subsequent systemic anticancer therapy to permit the detection of any delayed TEAEs.

Patients who discontinue study treatment for reasons other than progressive disease (PD) will complete the EOT visit and continue PFS follow-up Q4W from the EOT visit until the occurrence of PD, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 6.5.4), whichever occurs first. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

The Bayesian Optimal Interval (BOIN) design (Liu and Yuan 2015) will be implemented for dose escalation/de-escalation. The target toxicity rate for MTD is set to be $\phi = 0.25$ for MM maintenance and RRMM doublets and $\phi = 0.33$ for RRMM triplets, unless otherwise specified. A total of approximately 120 DLT-evaluable patients will be enrolled: approximately 18 for MM maintenance (Arm 1), approximately 66 for RRMM doublet combinations, and approximately 36 for RRMM triplet combinations.

The operating characteristics of the BOIN design evaluated with 1000 simulations assuming various distributions of toxicity across dose levels are presented in Appendix I.

6.2 Overview of Combination Therapy Groups and Dose Regimens

6.2.1 Group 1: MM Maintenance

6.2.1.1 Arm 1 Modakafusp alfa and Lenalidomide in MM After ASCT

Modakafusp alfa IV infusions in combination with lenalidomide PO will be administered on a 28-day (4-week) cycle (Table 6.a). Modakafusp alfa will be given on Day 1.

The following dose levels and schedules in treatment Arm 1 will be evaluated during phase 1b guided by BOIN design:

- Dose level -1 will consist of modakafusp alfa 60 mg IV on Day 1 and lenalidomide 10 mg PO QD continuously (Days 1 to 28).
- Dose level 0 (starting dose) will consist of modakafusp alfa 80 mg IV on Day 1 and lenalidomide 10 mg PO QD continuously (Days 1 to 28).
- Dose level 1 will consist of modakafusp alfa 120 mg IV on Day 1 and lenalidomide 10 mg PO QD continuously (Days 1 to 28).
- Dose level 2 will consist of modakafusp alfa 240 mg IV on Day 1 and lenalidomide 10 mg PO QD continuously (Days 1 to 28).

After 3 cycles of maintenance therapy, the dose of lenalidomide, per label, can be increased to 15 mg QD if tolerated.

Other dosing schedules may be explored on the basis of emerging data.

Patients in the MM maintenance group may continue to receive modakafusp alfa in combination with lenalidomide until disease progression, unacceptable toxicity, or to a maximum of 2 years for MRD[-] patients, whichever occurs first. Patients who remain MRD-positive with demonstrated clinical benefit after 2 years of maintenance therapy may continue treatment beyond 2 years with agreement of the sponsor/designee.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 6.a Arm 1: Modakafusp Alfa and Lenalidomide Dosing Schedule

	Cycle 1 and Later			
	Day 1	Day 8	Day 15	Day 22
Modakafusp Alfa IV (mg)	60, 80, 120 or 240 mg	-	-	-
Lenalidomide PO (mg)	10 mg QD continuously (Days 1 to 28) *			

IV: intravenous(ly); PO: oral(ly); QD: once daily.
* After 3 cycles of maintenance therapy, the dose of lenalidomide, per label, can be increased to 15 mg QD if tolerated.

6.2.2 Group 2: RRMM Doublets

Because of the predicted overlapping toxicities, the study will initially determine the safety and tolerability of modakafusp alfa as part of doublet combination therapy.

The doublet combinations (Arms 2 to 4) will consist of a dose escalation/de-escalation of multiple doublet combination arms guided by BOIN design. This part of the study is designed to determine the recommended dose of modakafusp alfa and the recommended dose of the combination agent, including, but not limited to, bortezomib and pomalidomide, for the respective triplet combination escalation/de-escalation starting dose within the range of approved dosage in the label.

The doublet schedules to be evaluated during this study include, but are not limited to, those described in Sections 6.2.2.1 through 6.2.2.3.

6.2.2.1 Arm 2 MP in RRMM

Modakafusp alfa IV infusions in combination with pomalidomide PO will be administered on a -28-day (4-week) cycle (Table 6.b). Modakafusp alfa will be given Q4W.

- Dose level -1 will consist of modakafusp alfa 60 mg IV on Day 1 and pomalidomide 4 mg PO on Days 1 to 21.*
- Dose level 0 (starting dose) will consist of modakafusp alfa 80 mg IV on Day 1 and pomalidomide 4 mg PO on Days 1 to 21.*
- Dose level 1 will consist of modakafusp alfa 120 mg IV on Day 1 and pomalidomide 4 mg PO on Days 1 to 21.*
- Dose level 2 will consist of modakafusp alfa 240 mg IV on Day 1 and pomalidomide 4 mg PO on Days 1 to 21.*

Other dosing regimens (eg, pomalidomide 2 or 3 mg) and schedules may be explored the basis of emerging data.

* Pomalidomide 2 mg (Day 1 through Day 21 of each 28-day cycle) and pomalidomide 3 mg (Day 1 through Day 21 of each 28-day cycle) may be explored in a new cohort on the basis of emerging data.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 6.b Arm 2: Modakafusp Alfa and Pomalidomide Dosing Schedule

	Cycle 1 and Later			
	Day 1	Day 8	Day 15	Day 22
Modakafusp alfa IV (mg)	60, 80, 120 or 240 mg	-	-	-
Pomalidomide PO (mg)	4 mg, Day 1 through Day 21 of each 28-day cycle. [a]			

IV: intravenous(ly); PO: oral(ly).
[a] Pomalidomide 2 mg (Day 1 through Day 21 of each 28-day cycle) and pomalidomide 3 mg (Day 1 through Day 21 of each 28-day cycle) may be explored in a new cohort on the basis of emerging data.

6.2.2.2 Arm 3 MV in RRMM

Modakafusp alfa IV infusion in combination with SC bortezomib will be administered in a 28-day (4-week) cycle (Table 6.c). Modakafusp alfa will be given Q4W.

- Dose level -1 will consist of modakafusp alfa 60 mg IV on Day 1 and bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22.
- Dose level 0 (starting dose) will consist of modakafusp alfa 80 mg IV on Day 1 and bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22.
- Dose level 1 will consist of modakafusp alfa 120 mg IV on Day 1 and bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22.
- Dose level 2 will consist of modakafusp alfa 240 mg IV on Day 1 and bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22.

Bortezomib will be administered 1.3 mg/m^2 SC on Days 8, 15, and 22 for the first 8 cycles and subsequently on Days 8 and 22 (Table 6.c). Other dosing regimens and schedules may be explored on the basis of emerging data.

At dose level 0, the first 3 patients of the first cohort must meet the following inclusion criterion: creatinine clearance ≥60 mL/min. If no renal safety events are observed during Cycle 1 in the first 3 patients (dose level 0), subsequent patients may be enrolled with a creatinine clearance ≥30 mL/min at screening. Enrollment for the first 3 patients will be staged; the next patient will be enrolled after the previous patient has finished Cycle 2 Day 8.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 6.c Modakafusp Alfa and Bortezomib Dosing Schedule

	Cycle 1 Through Cycle 8			
	Day 1	Day 8	Day 15	Day 22
Modakafusp alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Bortezomib SC (mg/m^2)	-	1.3	1.3	1.3
	Cycle 9 and Later			
	Day 1	Day 8	Day 15	Day 22
Modakafusp alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Bortezomib SC (mg/m^2)	-	1.3	-	1.3

IV: intravenous(ly); SC: subcutaneous(ly).

6.2.2.3 Arm 4 MK in RRMM (Closed to Enrollment)

This arm was closed after 3 patients were enrolled at dose level 0. Dose level 0 (starting dose) consisted of modakafusp alfa 80 mg IV on Day 1 and carfilzomib IV on Days 1, 8, and 15 (at an initial dose of 20 mg/m^2 on Cycle 1 Day 1 then at 70 mg/m^2 starting Cycle 1 Day 8). See Section 4.2.4.4. for further details.

6.2.3 Group 3: RRMM Triplets

Once the safety and tolerability of modakafusp alfa as part of doublet combination therapy is evaluated, the study is designed to determine the safety and tolerability of modakafusp alfa as part of triplet combination therapy (Arms A and D) based on the emerging data from the Group 2 doublet arms. Triplet combinations will consist of a dose escalation/de-escalation phase of triplet combination arms guided by the doublet combination data, modakafusp alfa/daratumumab data from TAK-573-2001, and the BOIN design. This part of the study is designed to determine the recommended triplet therapy modakafusp alfa dose and recommended dose of the 2 associated combination agents.

Treatment cycle duration is 28 days. Modakafusp alfa in combination with associated agents will be administered until disease progression or unacceptable toxicity, whichever comes first. Other dosing schedules may be explored on the basis of emerging data.

The triplet schedules to be evaluated during phase 1b include, but are not limited to, those described in Sections 6.2.3.1 through 6.2.3.2.

6.2.3.1 Arm A MPV in RRMM

Modakafusp alfa IV infusions in combination with bortezomib SC and pomalidomide PO will be administered on a 28-day (4-week) cycle (Table 6.d). Modakafusp alfa will be given Q4W.

- Dose level -1 will consist of modakafusp alfa IV 60 mg IV on Day 1 with bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22 and pomalidomide 4 mg PO on Days 1 to 21.
- Dose level 0 will consist of modakafusp alfa IV 80 mg IV on Day 1 with bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22 and pomalidomide 4 mg PO on Days 1 to 21.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Dose level 1 will consist of modakafusp alfa IV 120 mg IV on Day 1 with bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22 and pomalidomide 4 mg PO on Days 1 to 21.
- Dose level 2 will consist of modakafusp alfa IV 240 mg IV on Day 1 with bortezomib 1.3 mg/m^2 SC on Days 8, 15, and 22 and pomalidomide 4 mg PO on Days 1 to 21.

Bortezomib will be administered on 1.3 mg/m^2 SC on Days 8, 15, and 22 for the first 8 cycles and subsequently on Days 8 and 22.

The starting dose will be the lowest dose of modakafusp alfa doublet RP2D (60, 80, 120, or 240 mg). Other dosing schedules may be explored on the basis of emerging data.

Other dosing regimens (eg, pomalidomide 2 or 3 mg) and schedules may be explored on the basis of emerging data.

Table 6.d Modakafusp Alfa, Bortezomib and Pomalidomide Dosing Schedule

	Cycle 1 Through Cycle 8			
	Day 1	Day 8	Day 15	Day 22
Modakafusp alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Bortezomib SC (mg/m^2)	-	1.3	1.3	1.3
Pomalidomide PO (mg)	4 mg, Day 1 through Day 21 of each 28-day cycle. [a]			
	Cycle 9 and Later			
	Day 1	Day 8	Day 15	Day 22
Modakafusp alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Bortezomib SC (mg/m^2)	-	1.3	-	1.3
Pomalidomide PO (mg)	4 mg, Day 1 through Day 21 of each 28-day cycle. [a]			

IV: intravenous(ly); PO: oral(ly); SC: subcutaneous(ly).

[a] Pomalidomide 2 mg (Day 1 through Day 21 of each 28-day cycle) and pomalidomide 3 mg (Day 1 through Day 21 of each 28-day cycle) may be explored in a new cohort on the basis of emerging data.

6.2.3.2 Arm D MDR in RRMM

Modakafusp alfa IV infusions in combination with pomalidomide PO and daratumumab SC will be administered on a 28-day (4-week) cycle (Table 6.e). Modakafusp alfa will be given Q4W.

- Dose level -1 will consist of modakafusp alfa IV 60 mg IV on Day 1 with daratumumab 1800 mg SC and pomalidomide 4 mg PO on Days 1 to 21.
- Dose level 0 will consist of modakafusp alfa IV 80 mg IV on Day 1 with daratumumab 1800 mg SC and pomalidomide 4 mg PO on Days 1 to 21.
- Dose level 1 will consist of modakafusp alfa IV 120 mg IV on Day 1 with daratumumab 1800 mg SC and pomalidomide 4 mg PO on Days 1 to 21.
- Dose level 2 will consist of modakafusp alfa IV 240 mg IV on Day 1 with daratumumab 1800 mg SC and pomalidomide 4 mg PO on Days 1 to 21.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Daratumumab 1800 mg SC is administered on Days 1, 8, 15, and 22 of Cycles 1 and 2, then on Days 1 and 15 of Cycles 3 to 6, then on Day 1 thereafter. No dose reduction is permitted for daratumumab. The starting dose of modakafusp alfa will be the lowest dose of modakafusp alfa doublet RP2D (60, 80, 120, or 240 mg).

Other dosing regimens (eg, pomalidomide 2 or 3 mg) and schedules may be explored on the basis of emerging data.

Table 6.e Arm D: Modakafusp Alfa, Daratumumab and Pomalidomide Dosing Schedule

	Cycle 1 & Cycle 2			
	Day 1	Day 8	Day 15	Day 22
Modakafusp Alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Daratumumab SC (mg)	1800	1800	1800	1800
Pomalidomide (PO)	4 mg, Day 1 through Day 21 of each 28-day cycle.*			
	Cycle 3 to Cycle 6			
	Day 1	Day 8	Day 15	Day 22
Modakafusp Alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Daratumumab SC (mg)	1800	-	1800	-
Pomalidomide (PO)	4 mg, Day 1 through Day 21 of each 28-day cycle.*			
	Cycle 7 and Later			
	Day 1	Day 8	Day 15	Day 22
Modakafusp Alfa IV (mg)	60, 80, 120, or 240 mg	-	-	-
Daratumumab SC (mg)	1800	-	-	-
Pomalidomide (PO)	4 mg, Day 1 through Day 21 of each 28-day cycle.*			

IV: intravenous(ly); PO: oral(ly); SC: subcutaneous(ly).
* Pomalidomide 2 mg (Day 1 through Day 21 of each 28-day cycle) and pomalidomide 3 mg (Day 1 through Day 21 of each 28-day cycle) may be explored in a new cohort on the basis of emerging data.

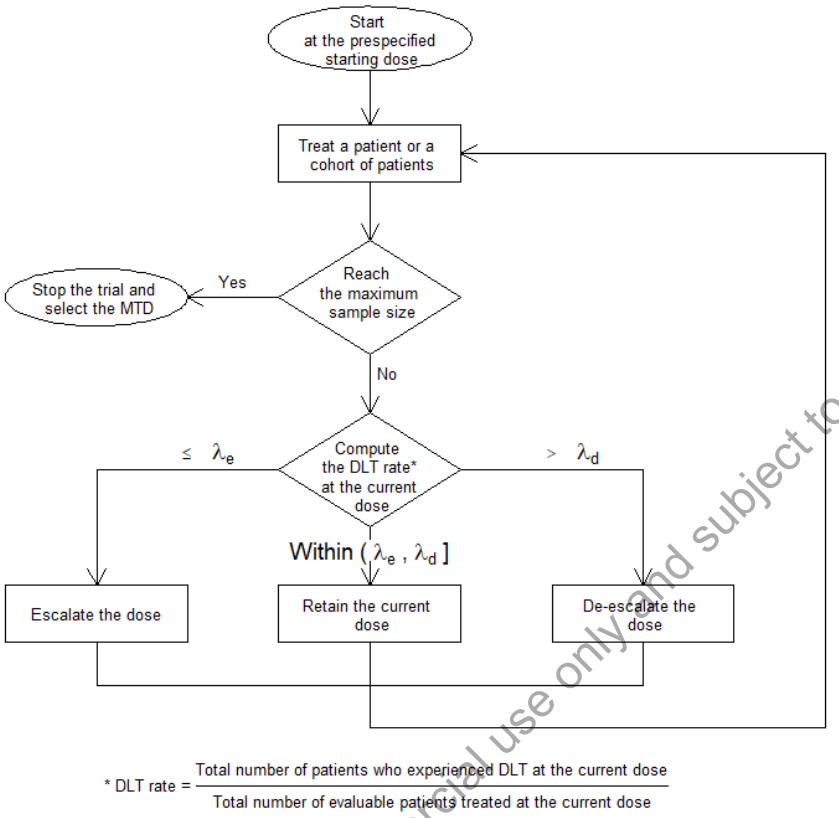
6.3 Dose Escalation/De-escalation

The BOIN design (Liu and Yuan 2015) will be implemented to guide the dose escalation/de-escalation (Figure 6.b). The target toxicity rate for MTD is set to be $\phi = 0.25$ for MM maintenance as well as RRMM doublets and $\phi = 0.33$ for RRMM triplets, unless otherwise specified. Further details and simulations are found in Appendix I.

Patients will be enrolled and treated in cohort sizes of approximately 3. The starting dose will need to treat at least 3 DLT-evaluable patients. It is estimated that a total of approximately 120 DLT-evaluable patients will be enrolled: approximately 18 for MM maintenance (Arm 1), approximately 66 for RRMM doublet combinations, and approximately 36 for RRMM triplet combinations.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Figure 6.b Flowchart for Study Conduct Using the BOIN Design



BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; MTD: maximum tolerated dose; λ_d: DLT rate de-escalation boundary; λ_e: DLT rate escalation boundary.

6.3.1 Group 1: MM Maintenance

The BOIN design will be used for dose escalation/de-escalation for MM maintenance. The target toxicity rate is set to be $\phi = 0.25$. Patients will be enrolled and treated in cohorts of approximately 3. The starting dose will need to treat at least 3 evaluable patients. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j. When the lowest dose is eliminated, that arm will be stopped for safety. It is estimated that approximately 18 DLT-evaluable patients will be enrolled.

The BOIN design will be implemented following the steps described below:

1. Patients in the first cohort are treated at a starting dose with at least 3 evaluable patients.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

2. A dose is assigned to the next cohort of patients according to the rule below:
   - If the observed DLT rate at the current dose is $\leq \lambda_e = 0.197$, escalate the dose to the next higher level.
   - If the observed DLT rate at the current dose is $> \lambda_d = 0.298$, de-escalate the dose to the next lower dose level.
   - Otherwise, stay at the current dose.
3. Repeat Step 2 until the maximum sample size of 18 is reached or stop the arm if the number of DLT-evaluable patients treated at the current dose level reaches 6 and the decision is made to stay at the current dose. Table 6.f presents the BOIN design decision rules for Group 1 MM maintenance.

Table 6.f BOIN Design Decision Rule for Group 1: MM Maintenance and Group 2: RRMM Doublets

Number of evaluable patients treated	1	2	3	4	5	6	7	8	9
Escalate if number of DLT ≤	0	0	0	0	0	1	1	1	1
Deescalate if number of DLTs ≥	1	1	1	2	2	2	3	3	3
Eliminate if number of DLTs ≥	NA	NA	3	3	3	4	4	4	5

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; NA: not applicable, dose cannot be eliminated before 3 evaluable patients are treated; RRMM: relapsed/refractory multiple myeloma.

Note: Number of DLTs is the number of patients with at least 1 DLT. If none of the actions (ie, escalate, de-escalate or eliminate) are triggered, stay at the current dose for treating the next cohort of patients.

6.3.2 Group 2: RRMM Doublets

The BOIN design will be implemented for dose escalation/de-escalation for RRMM doublets in the same way as in the MM maintenance group. The BOIN design decision rules are presented in Table 6.f.

For Arm 2 (modakafusp + pomalidomide 4 mg), other dosing and/or schedules for pomalidomide (eg, 2 mg, 3 mg) may be explored on the basis of emerging data. If a different dose level of pomalidomide needs to be explored, the previous BOIN design will be considered to have stopped early, and a new BOIN design will be started for modakafusp alfa dose escalation/de-escalation with the new fixed pomalidomide dosing.

Approximately 36 DLT-evaluable patients will be enrolled in the RRMM doublet combinations. Patients will be enrolled and treated in cohorts of approximately 3. At least 3 DLT-evaluable patients need to be treated at the starting dose prior to escalating to the next dose level, unless 2 DLTs have been observed in the first 2 patients.

6.3.3 Group 3: RRMM Triplets

After the doublet RP2D is determined in RRMM doublets, dose escalation of modakafusp alfa in triplet combinations will begin. BOIN design will be employed to provide statistical guidance for

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

the dose escalation/de-escalation decisions. The target toxicity rate for the MTD is set to be $\phi = 0.33$. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.33 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j. When the lowest dose is eliminated, stop that arm for safety. It is estimated that approximately 36 DLT-evaluable patients will be enrolled.

The escalation/de-escalation will be conducted in steps as follows:

Patients in the first cohort are treated at the starting dose level with at least 3 evaluable patients.

Assign a dose to the next cohort of patients according to the rule below:

- If the observed DLT rate at the current dose is $\leq \lambda_e = 0.260$, escalate the dose to the next higher level.
- If the observed DLT rate at the current dose is $> \lambda_d = 0.395$, de-escalate the dose to the next lower dose level.
- Otherwise, stay at the current dose.

Repeat Step 2 until the maximum sample size of 18 is reached or stop that arm if the number of evaluable patients treated at the current dose reaches 9 and the decision is to stay at the current dose. Table 6.g presents the BOIN design decision rules for Group 3.

Table 6.g BOIN Design Decision Table for Group 3: RRMM Triplets

Number of evaluable patients treated	1	2	3	4	5	6	7	8	9	10	11	12
Escalate if number of DLTs ≤	0	0	0	1	1	1	1	2	2	2	2	3
Deescalate if number of DLTs ≥	1	1	2	2	2	3	3	4	4	4	5	5
Eliminate if number of DLTs ≥	NA	NA	3	3	4	4	5	5	6	6	7	7

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; NA: not applicable, a dose cannot be eliminated before treating 3 evaluable patients; RRMM: relapsed/refractory multiple myeloma.
Note: Number of DLTs is the number of patients with at least 1 DLT. If none of the actions (ie, escalate, de-escalate or eliminate) are triggered, stay at the current dose for treating the next cohort of patients.

Based on emerging data and/or and discussions between the sponsor and the investigators, the following measures are all permissible if such measures are needed for patient safety or for a better understanding of dose-related toxicity, exposure, or pharmacodynamics:

- More conservative dose escalation.
- Evaluation of intermediate doses.
- Different dose schedule(s), alternative dose combinations, and/or dose schedule(s).
- Expansion of an existing dose level.

Before initiating dosing at the next dose level, when safety data are available for all patients in the current dose level, key safety data will be reviewed and evaluated by the study team

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

consisting of sponsor representatives and investigators who will review the safety of all treated patients and make decisions regarding dose escalation. All decisions will be documented in writing. Any decision to modify the dose escalation scheme in a direction that increases the already approved frequency of administration or dose escalation steps will be communicated to institutional review boards (IRBs), and the protocol will be amended accordingly.

Details about the management of dose escalation decisions can be found in the cohort management plan.

6.3.4 [redacted]

[redacted]

6.4 Number of Patients

Approximately 120 patients will be enrolled into the following groups:

- Group 1 (MM maintenance; Arm 1): Approximately 18 patients will be enrolled.
- Group 2 (RRMM doublets): Approximately 66 patients will be enrolled.
- Group 3 (RRMM triplets): Approximately 36 patients will be enrolled.

Details on the definition of evaluable patients and sample size are given in Sections 13.1.1 and 13.3, respectively.

The study is planned to be conducted globally at approximately 50 investigational sites.

Patients who are determined to be DLT nonevaluable will be replaced. The definition of DLT evaluable patients is provided in Section 8.5.1.

Property of Takeda. For non-commercial use only, subject to the applicable Terms of Use

6.5 Duration of the Study

6.5.1 Duration of an Individual Patient's Study Participation

In the Group 1 MM maintenance, MRD[-] patients may receive modakafusp alfa in combination with lenalidomide for up to 2 years or until they experience disease progression or unacceptable toxicity, or until any other discontinuation criterion is met, whichever occurs first. MRD-positive patients at 2 years of maintenance may continue treatment with the agreement of the sponsor/designee.

In the Group 2 RRMM doublets and Group 3 RRMM triplets, patients may receive modakafusp alfa in combination with associated agents until disease progression or unacceptable toxicity occurs or until any other discontinuation criterion is met (Section 9.11), whichever occurs first.

Patients will be evaluated approximately 30 days (EOT visit) after the last dose of treatment or before the start of subsequent alternative anticancer therapy to permit the detection of any delayed TEAEs.

For patients who discontinue modakafusp alfa in combination with associated agents before PD, disease evaluation should continue to be performed as specified in the SOEs (Appendix A). Patients who discontinue for PD will be followed for survival after documented PD for up to 12 months after the last patient discontinues or completes treatment, or until loss of follow-up, consent withdrawal, death, study termination, or until ≥50% of patients in the cohort have died, whichever occurs first.

Patients who discontinue for reasons other than PD will continue PFS follow-up Q4W from the EOT visit until the occurrence of PD, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 6.5.4), or until 6 months after the discontinuation of study treatment, whichever occurs first. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

6.5.2 Total Study Duration

The study is expected to enroll patients for approximately 24 to 30 months and continue follow-up for a total duration of approximately 5 years.

6.5.3 Posttrial Access

At the conclusion or termination of the study (Section 6.5.4) or termination of a treatment arm in the study, ongoing patients who are continuing to experience clinically important benefit from modakafusp alfa in combination with assigned agent(s), have no locally available comparable or satisfactory alternative therapeutic option, and would be negatively affected without continued access to modakafusp alfa, in the opinion of the investigator and confirmed by the sponsor, may continue to receive modakafusp alfa through the posttrial access (PTA) program (where permitted by local regulations).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

6.5.3.1 Duration of PTA

Conditions under which the sponsor may terminate PTA to modakafusp alfa:

- Patient has completed the protocol-defined course or duration of therapy as defined for the PTA program.
- The benefit-risk profile is no longer favorable (eg, their disease has progressed, or treatment is no longer tolerable).
- Modakafusp alfa becomes commercially available or another appropriate access mechanism becomes available.
- An appropriate alternative therapy becomes available.
- Marketing authorization has been rejected in the respective country.
- Development of modakafusp alfa is suspended or ceased, or the sponsor cannot adequately supply modakafusp alfa.
- After a predetermined period agreed on by the sponsor with input from investigators before the start of the study, documented in protocol and informed consent.

6.5.3.2 Combination Agents

Only modakafusp alfa, which should be used in combination only as part of a study-specified combination, will be provided by the PTA program, unless any country-specific laws and regulations require the sponsor to provide combination therapies as part of PTA.

6.5.4 Definition of End of Study/Study Completion and Planned Reporting

The final analysis for the clinical study report will be conducted after all patients enrolled in the study have completed all study assessments as outlined in the SOEs or have withdrawn from the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or the sponsor (Takeda), there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient, incomplete, and/or unevaluable data.
- Determination of efficacy based on an interim analysis.
- Plans to modify, suspend, or discontinue development of the study drug.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Should the study be closed prematurely, the site will no longer be able to access the electronic data capture (EDC) application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. Any devices provided to access the EDC application will be returned to Takeda once the site's participation in the study has concluded.

Takeda must notify the competent authorities and independent ethics committees (IECs) of any member state where the study is being conducted within 15 days of premature study closure and provide the reasons for study closure.

Within 90 days of ending the study, the sponsor will notify the competent authorities and the IECs in all member states where the study was being carried out. Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Adult patient aged ≥18 years at the time of the informed consent.
2. All patients in Group 1 (MM maintenance: modakafusp alfa/lenalidomide) only must have:
   a) MM based on standard IMWG diagnostic criteria (Appendix G).
   b) Undergone ASCT for the treatment of MM within 12 months of the start of induction therapy and completed ASCT within 180 days before enrollment (regardless of the lines of treatment). Consolidation cycles are allowed. Tandem transplant is allowed.
   c) Not started lenalidomide maintenance before enrollment. Time to initiation of maintenance therapy: Patients may start maintenance therapy as early as 60 days after transplantation and up to 180 days after transplantation or consolidation.
   d) MRD positive after ASCT (MRD assessed at a threshold of 10^{-5} by local SOC methods or central assessment, if a prior local MRD assessment had not been performed).
   e) No prior progression after initial therapy (at any time before starting maintenance). Patients whose induction therapy was changed due to suboptimal response or toxicity will be eligible if they do not meet criteria for progression. In addition, no more than 2 regimens will be allowed before ASCT, excluding dexamethasone alone.
   f) No prior allogeneic hematopoietic stem cell transplant or solid organ transplant.
   g) Recovered to Grade ≤1 ASCT-related toxicities from the reversible effects of ASCT (except for alopecia and amenorrhea).
3. All patients in Groups 2 and 3 (RRMM doublets and RRMM triplets) must have
   a) Measurable disease, defined as at least 1of the following:

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Serum M-protein ≥0.5 g/dL (≥5 g/L) on serum protein electrophoresis (SPEP).
- Urine M-protein ≥200 mg/24 hours on urine protein electrophoresis (UPEP).
- Serum FLC assay result with an involved FLC level ≥10 mg/dL (≥100 mg/L), provided the serum FLC ratio is abnormal (per IMWG criteria).

b) A confirmed diagnosis of MM according to IMWG criteria (Appendix G) with documented disease progression in need of additional therapy as determined by the investigator.

c) For Group 2 RRMM doublet arms only: Patients who have received at least 3 prior lines of antimyeloma therapy, including at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb drug, or who are triple refractory to a PI, and IMiD, and an anti-CD38 mAb drug regardless of the number of prior line(s) of therapy.

d) For Group 3 RRMM triplet arms only: Patients who have received 1 to 3 prior lines of antimyeloma therapy, including at least 1 PI and 1 IMiD, and who are not refractory* to the combination partners.

e) For anti-CD38 arms, forced expiratory volume in 1 second (FEV_1) ≥50% predicted by pulmonary function testing.

NOTES:

A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens. (For example, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by a stem cell transplantation, consolidation, and maintenance is considered 1 line.)

* Refractory myeloma is defined as disease that is nonresponsive while the patient is receiving primary or salvage therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least a minimal response or the development of PD while on therapy (Rajkumar et al. 2011).

4. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at screening (Appendix H).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

5. The patient has adequate organ function at screening as determined by the laboratory values shown in Table 7.a:

Table 7.a Laboratory Values Required for Enrollment

ANC [a]	$\geq 1000/mm^3$ ($\geq 1.0 \times 10^9/L$)
Platelets [a]	$\geq 75{,}000/mm^3$ ($\geq 75 \times 10^9/L$)
Hemoglobin	≥8.0 g/dL
Estimated creatinine clearance	≥30 mL/min (Cockcroft-Gault formula) [b]
Total serum bilirubin	≤2.0 × ULN; an exception for patients with Gilbert's syndrome may be granted after discussion with the sponsor.
Liver transaminases (ALT/AST)	≤3.0 × ULN

ALT: alanine aminotransferase: ANC: absolute neutrophil count; AST: aspartate aminotransferase; ULN: upper limit of normal.

[a] Without ongoing growth factor for at least 3 days before Day 1 or transfusion support for at least 1 week before Day 1.

[b] Estimated creatinine clearance ≥60 mL/min (Cockcroft-Gault formula) for the first 3 patients in Arm 3.

6. The patient has recovered from adverse reactions to prior myeloma treatment or procedures (eg, chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE, Version 5.0 Grade ≤1 or baseline treatment or have the toxicity established as sequela, except for sensory or motor neuropathy, which should have recovered to Grade ≤2 or baseline (Grade 1 for the bortezomib arm).
7. Patients with uterus and ovary(ies) who:
   - Are postmenopausal (amenorrheic) for at least 2 years 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 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer, OR
     - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the time of signing of the informed consent through 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

  - Agree not to donate an egg or eggs (ova) during the study and for 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer.

- Must also adhere to guidelines to any treatment-specific pregnancy prevention program, if applicable, as appropriate in the country (eg, Risk Evaluation and Mitigation Strategy [REMS] or Pregnancy Prevention Program for lenalidomide or pomalidomide).

8. Patients with testis(es), even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject, from the signing of the informed consent form (ICF) through 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).
   - Agree not to donate sperm from the signing of the ICF through 7 days after the last dose of modakafusp alfa or through the period defined by label for combination agents, whichever is longer.
   - Must also adhere to guidelines to any treatment-specific pregnancy prevention program, if applicable, as appropriate in the country (eg, REMS or Pregnancy Prevention Program for lenalidomide or pomalidomide).

9. The minimal interval between the last dose of any of the following treatments/procedures and the first dose of the study treatment must be at least those shown below:

Chemotherapy, including PIs and IMiDs	14 days
Bispecific antibodies	28 days
Any investigational anticancer product	28 days
Corticosteroid therapy for myeloma.	7 days
Radiation therapy for localized bone lesions: Prophylactic localized ("spot") radiation for areas of pain is allowed.	7 days
Major surgery: Patients should be fully recovered from any surgically-related complications.	28 days
Plasmapheresis	28 days
Inoculation with any live virus (eg, varicella)	30 days

IMiD: immunomodulatory drug; PI: proteosome inhibitor.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

10. The patient has suitable venous access for safe drug administration and the study-required blood sampling.
11. Voluntary written or electronic consent (eConsent) must be given before performance of any study-related procedure that is not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. 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.

7.2 Exclusion Criteria

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

1. The patient is currently participating in another MM interventional study, including other clinical trials with investigational agents (including investigational vaccines or investigational medical device for disease under study) throughout the duration of this study.
2. The patient received previous treatment with modakafusp alfa.
3. The patient has a diagnosis of primary amyloidosis, Waldenström disease, monoclonal gammopathy of undetermined significance or smoldering MM per IMWG criteria or standard diagnostic criteria, plasma cell leukemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or lymphoplasmacytic lymphoma.
4. The patient has been diagnosed with another malignancy within the previous 3 years, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, cervical carcinoma in situ, resected colorectal adenomatous polyps, breast cancer in situ, or other malignancy for which the patient is not on active anticancer therapy and that in the opinion of the local investigator, with concurrence with the sponsor, is considered cured with minimal risk of recurrence within 3 years.
5. The patient has evidence of CNS involvement and/or meningeal involvement due to MM exhibited during screening.
6. The patient has a known severe allergic or anaphylactic reactions to human recombinant proteins or excipients used in the modakafusp alfa formulation or to the study combination agents, the study medications, their analogs, or excipients in the various formulations of any agent per the prescribing information.
7. The patient has a history of treatment discontinuation due to treatment-related toxicity to the combination agent per the investigator. For lenalidomide arm: The patient is intolerant to lenalidomide.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

8. The patient is unable to take label-recommended/required prophylaxis needed for combination agents (eg, antithrombotic prophylaxis for lenalidomide and pomalidomide, antiviral prophylaxis for PI).
9. The patient is unable or unwilling to swallow PO medication or to comply with the drug administration requirements, or gastrointestinal procedure that could interfere with the PO absorption or tolerance of PO combination agents.
10. The patient has a known history of seropositivity for HIV.
11. The patient is seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Patients with resolved infection (that is, participants who are HBsAg negative but positive for antibodies to hepatitis B core antigen and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. Exception: Patients with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and, a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
12. The patient has a known history of seropositivity for hepatitis C (anti-hepatitis C virus antibody positive or anti-hepatitis C virus–RNA quantitation positive). Exception: Patients with a sustained virologic response with undetectable HCV RNA level at least 12 weeks after completion of antiviral therapy.
13. For bortezomib arms: patient received a strong CYP3A4 inducer within 5 half-lives prior to randomization.
14. The patient has a chronic condition requiring the use of systemic corticosteroids >10 mg/d of prednisone or equivalent in addition to any required corticosteroids for the treatment of MM.
15. The patient has a QTcF (QT interval corrected with Fridericia correction method) >480 ms (Grade ≥2).
16. Patient has a history of acute myocardial infarction within 5 months from enrollment or has electrocardiographic (ECG) abnormalities during screening that are deemed medically relevant by the investigator.
17. Patient has congestive heart failure (New York Heart Association Grade ≥II), cardiac myopathy, active ischemia, or any other uncontrolled cardiac conditions such as angina pectoris, clinically significant arrhythmias requiring therapy (eg, anticoagulants), or clinically significant uncontrolled hypertension.
18. Patient has a high risk of hemorrhage such as uncontrolled chronic bleeding disorder or is currently being treated with therapeutic anticoagulation. Antithrombotic prophylaxis for lenalidomide and pomalidomide is authorized.
19. The patient has any concurrent or uncontrolled medical, comorbid, or psychiatric condition or disease that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

20. The patient has a psychiatric illness/social circumstance that would limit compliance with study requirements and substantially increase the risk of TEAEs or compromised ability to provide written informed consent.
21. Patient is lactating and breastfeeding or has a positive urine or serum pregnancy test during the screening period or a positive urine or serum pregnancy test before first dose of study drug.

8.0 STUDY DRUG

8.1 Study Drug Administration

8.1.1 Modakafusp Alfa

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 sub investigator(s).

Modakafusp will be administered by infusion over 1 hour (±10 minutes). Any decrease in infusion duration must be discussed with and agreed upon by the sponsor.

In the combination arms with SC combination agents (eg, bortezomib, daratumumab), the combination agent will be administered before modakafusp alfa on days on which both agents are given on the same visit day. At least 30 minutes should elapse between the completion of the injection of the first study drug and the initiation of the infusion of modakafusp alfa.

In the combination arms with PO combination agents (eg, lenalidomide, pomalidomide), the PO combination agent should be administered at about the same time each day. When both modakafusp alfa and the PO combination agent are given on the same visit day, the PO combination agent should not be taken at the same time as modakafusp alfa (at least 30 minutes should elapse between the administration of the 2 drugs).

If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per the investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of the infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See pharmacy manual for additional guidance.

8.1.1.1 Premedications

It is mandatory that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing. Any decision to stop premedications must be discussed with and agreed upon by the sponsor.

Before each infusion of modakafusp alfa, patients must receive the following premedications unless contraindicated per investigator discretion:

- Corticosteroid IV or PO (methylprednisolone 100 mg, dexamethasone 20 mg, or equivalent). If a patient does not experience a significant IRR, the dose of methylprednisolone may be

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

decreased to 60 mg (or dexamethasone to 12 mg) after Cycle 3. Intermediate- or long-lasting steroids of equivalent dose can be substituted.

- Acetaminophen 650 to 1000 mg PO.
- Antihistamine: Diphenhydramine 25 to 50 mg PO or equivalent. A second-generation antihistamine (eg, cetirizine) may be substituted if a first-generation antihistamine is not tolerated or available.

Montelukast 10 mg PO and/or H2 blockers may be given to patients who are intolerant to antihistamines or for whom antihistamines are ineffective or not available.

Premedications must be administered before daratumumab SC to comply with the daratumumab label. When daratumumab is given during the same visit as modakafusp alfa, administer the modakafusp alfa–specific premedications only prior to the daratumumab. Do not administer daratumumab-specific premedications on modakafusp alfa administration days (CxD1) when patients have received modakafusp alfa premedication.

8.1.1.2 Postinfusion Medication

Administer 20 to 25 mg of prednisone or 4 mg of dexamethasone PO or equivalent on the first and second days after all full-dose infusions (CxD2 and CxD3). Other concomitant medications can be administered per institutional protocols.

During all infusions and for at least 2 hours postdose, the patient should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage infusion reactions. See Section 8.7 for further information.

On days when both daratumumab and hyaluronidase-fihj and modakafusp alfa are given on the same visit day, administer the modakafusp alfa–specific postmedication only.

8.1.1.3 Prophylaxis Against Risk of Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylactic antiviral therapy such as acyclovir or valacyclovir should be initiated as clinically indicated or as recommended with specific combinations agents as described below.

8.1.2 Combination Agents

8.1.2.1 Lenalidomide Administration, Premedications and Prophylaxis

Lenalidomide 10 mg will be administered QD continuously (Days 1 to 28) per Section 6.2.1. After 3 cycles of maintenance therapy, the dose of lenalidomide, per label, can be increased to 15 mg QD if tolerated. Lenalidomide should be taken at about the same time each day. When both modakafusp alfa and lenalidomide are given on the same visit day, lenalidomide should not be administered at the same time as modakafusp alfa. (At least 30 minutes should elapse between the administration of the 2 drugs.)

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Usage should be in accordance with the precautions and instructions provided by the manufacturer. Additional drug description, preparation, storage, and handling instructions will be provided in the pharmacy manual.

Antithrombotic prophylaxis is recommended. The choice of regimen should be based on assessment of the patient's underlying risk factors. Monitoring of liver enzymes and thyroid function during therapy is recommended.

Lenalidomide is similar to thalidomide and may cause severe life-threatening birth defects. Mandatory adherence to guidelines to any treatment-specific pregnancy prevention program, if applicable, as appropriate in the country (eg, REMS or Pregnancy Prevention Program for lenalidomide) is required.

Participants with a uterus/ovary(ies) must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions, and for at least 4 weeks after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control beginning 4 weeks before initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 4 weeks after discontinuation of lenalidomide therapy.

Two negative pregnancy test results must be obtained before initiating therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours before the beginning of lenalidomide therapy. Pregnancy tests should then be obtained weekly during the first month, and monthly thereafter for participants with regular menstrual cycles, or every 2 weeks for participants with irregular menstrual cycles.

Drug Interactions

Digoxin: Lenalidomide may increase digoxin plasma levels. Periodically monitor digoxin plasma levels with concomitant lenalidomide therapy in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication.

Concomitant therapies that may increase the risk of thrombosis: Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving lenalidomide.

Warfarin: Close monitoring of PT and INR is recommended in patients with MM receiving lenalidomide and taking concomitant warfarin (Revlimid (lenalidomide) 2021).

8.1.2.2 Pomalidomide Administration, Premedications and Prophylaxis

The pomalidomide dose will be 4 mg PO on Days 1 through 21 of each 28-day cycle per Sections 6.2.2 and Section 6.2.3. Pomalidomide should be taken at about the same time each day. When both modakafusp alfa and pomalidomide are given on the same visit day, pomalidomide should not be administered at the same time as modakafusp alfa. (At least 30 minutes should elapse between the administration of the 2 drugs.)

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Usage should be in accordance with the precautions and instructions provided by the manufacturer. Additional drug description, preparation, storage, and handling instructions will be provided in the pharmacy manual.

Antithrombotic prophylaxis is recommended. The choice of regimen should be based on assessment of the patient's underlying risk factors. Monitoring of liver enzymes monthly is recommended.

For patients with hepatic impairment, reduce the dosage of pomalidomide per label.

Pomalidomide is similar to thalidomide and may cause severe life-threatening birth defects. Mandatory adherence to guidelines to any treatment-specific pregnancy prevention program, if applicable, as appropriate in the country (eg, REMS or Pregnancy Prevention Program for pomalidomide) is required.

Participants with a uterus/ovary(ies) must avoid pregnancy for at least 4 weeks before beginning pomalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control beginning 4 weeks before initiating treatment with pomalidomide, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of pomalidomide therapy.

Two negative pregnancy test results must be obtained before initiating therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours before prescribing pomalidomide therapy. Pregnancy tests should then be obtained weekly during the first month, and monthly thereafter for participants with regular menstrual cycles, or every 2 weeks for participants with irregular menstrual cycles.

Drug Interactions

Strong CYP1A2 Inhibitors: Avoid concomitant use of strong CYP1A2 inhibitors. If concomitant use of a strong CYP1A2 inhibitor is unavoidable, reduce pomalidomide dose per label (Pomalyst (pomalidomide) Capsules 2020).

8.1.2.3 Bortezomib Administration, Premedications and Prophylaxis

The bortezomib dose will be 1.3 mg/m^2 SC on Days 8, 15 and 22 of each 28-day cycle for the first 8 cycles and subsequently on Days 8 and 22 per Section 6.2.2 and Section 6.2.3. Use should be in accordance with the precautions and instructions provided by the manufacturer. Additional drug description, preparation, storage, and handling instructions will be provided in the pharmacy manual.

When administered SC, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least 1 inch from a recent site and never into areas that are tender, bruised, erythematous, or indurated.

Antiviral prophylaxis for herpes zoster reactivation is recommended.

For patients with hepatic impairment, adjust the starting dose of bortezomib per label.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Drug Interactions

Strong CYP3A4 Inducers: Avoid concomitant use of strong CYP3A4 Inducers.

Strong CYP3A4 Inhibitors: Closely monitor patients for signs of bortezomib toxicity with concomitant use of strong CYP3A4 inhibitors and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors per label (Velcade (bortezomib) for Injection 2019).

For the reconstitution/preparation of bortezomib, please refer to the prescribing information.

8.1.2.4 Daratumumab Administration, Premedications and Prophylaxis

8.1.2.4.1 Administration

The daratumumab dose will be 1800 mg SC on Days 1, 8, 15, and 22 of Cycles 1 and 2, then on Days 1 and 15 of Cycles 3 to 6, then on Day 1 thereafter per Section 6.2.3. No dose reduction is permitted for daratumumab. Usage should be in accordance with the precautions and instructions provided by the manufacturer. Additional drug description, preparation, storage, and handling instructions will be provided in the pharmacy manual.

Daratumumab and hyaluronidase-fihj will be administered before modakafusp alfa on days when both agents are given on the same visit day. At least 30 minutes should elapse between the completion of the injection of the first study drug and the initiation of the infusion of the second study drug.

Further information about SC daratumumab can be found in Section 4.3.4.

8.1.2.4.2 Premedications

Before each injection, patients will receive the following premedications approximately 1 to 3 hours before the daratumumab and hyaluronidase-fihj on each dosing day (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

- Methylprednisolone 100 mg (or approximate equivalent such as dexamethasone 20 mg) PO or IV for the initial injection. Consider reducing the dose of methylprednisolone to 60 mg (or approximate equivalent such as dexamethasone 12 mg) PO or IV following the second dose of daratumumab and hyaluronidase-fihj before subsequent injections.
- Antipyretics: PO acetaminophen (650 to 1000 mg).
- Antihistamines: PO or IV diphenhydramine (25 to 50 mg, or equivalent).

On days when both daratumumab and hyaluronidase-fihj and modakafusp alfa are given on the same visit day, administer the modakafusp alfa-specific premedications only.

8.1.2.4.3 Postmedication

Administer methylprednisolone 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid such as dexamethasone 4 mg) PO for 2 days starting the day after the

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

administration of daratumumab and hyaluronidase-fihj (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

On days when both daratumumab and hyaluronidase-fihj and modakafusp alfa are given on the same visit day, administer the modakafusp alfa–specific postmedication only.

If the patient does not experience a major systemic administration-related reaction after the first 3 doses of daratumumab and hyaluronidase-fihj, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid or corticosteroids required as a premedication/postmedication for the combination drug such as modakafusp alfa).

Note: For any patient with a history of chronic obstructive pulmonary disease, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids. Following the first 4 doses of daratumumab and hyaluronidase-fihj, consider discontinuing these additional postmedications if the patient does not experience a major systemic administration-related reaction (Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021).

8.1.2.4.4 Prophylaxis for Herpes Zoster Reactivation

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

8.2 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 will be recorded in the electronic case report forms (eCRFs) as specified in the SOEs (Appendix A). The following medications and procedures are permitted while the patient is receiving the study drug:

- Myeloid growth factors (eg, granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice. G-CSF is allowed to accelerate the recovery of neutropenia to enable the start of new cycle (Section 8.6.1.1).
- Patients should be transfused with RBCs and platelets as clinically indicated. Transfusions must be recorded in the concomitant procedure pages of the eCRF. Platelet transfusion should not be applied only for the purpose of meeting the treatment criterion of platelet count to start a new cycle.
- Concomitant treatment with bisphosphonates or antiosteolytic mAbs 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 (eg, for the treatment of asthma) are permitted.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Systemic steroids for acute management of pain, suspected or confirmed immune-mediated thrombocytopenia or other disease or treatment-related complications are permitted.
- Plasmapheresis.
- Intravenous immunoglobulin (IVIG) usage is acceptable for prolonged Grade 4 transfusion-dependent thrombocytopenia, hypogammaglobulinemia, or other investigator criteria if it is considered that there is an underlying autoimmune mechanism.
- Thrombopoietin agonists are also allowed for thrombocytopenia management at the investigator's discretion.

8.3 Prohibited Medications and Procedures

The following medications and procedures are prohibited during the study:

- Radiation therapy for disease under study. Local radiotherapy for bone pain is permitted after agreement with the sponsor and once PD is ruled out.
- Any investigational agent other than modakafusp alfa or the study combination agents, including agents that are commercially available for indications other than MM that are under investigation for the treatment of MM.
- Carfilzomib: Modakafusp alfa is contraindicated in combination with carfilzomib. See Section 4.2.4.4 for more information.
- Concomitant chronic corticosteroid administration of >10 mg of prednisone or equivalent unless given as treatment or prophylaxis for IRRs, as premedication for administration of certain blood products or for exacerbations of respiratory tract disorders, acute pain management, suspected or confirmed immune-mediated thrombocytopenia, if tumor flare is suspected, or as needed for other disease or treatment-related complications.
- Live vaccines are excluded within 30 days before the first administration of study treatment and for 90 days after completion of study treatment.

Please see Sections 8.2 and 8.7 and individual prescribing information for possible excluded medications, supplements, and dietary products for each combination agent.

8.4 List of European Union Auxiliary Medicinal Products Used in the Trial Other Than the Investigational Products

Below are required concomitant medications essential to the assessment of safety or efficacy of the investigational medicinal product, required rescue medications, and required prophylaxis and/or required challenge medications.

- Corticosteroids.
- Analgesics and antipyretics.
- Antihistamines.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Leukotriene receptor antagonists.
- Antivirals.
- Antithrombotic agents.

8.5 DLTs

Toxicity will be evaluated according to the NCI CTCAE, Version 5.0.

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

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

- Delay in the initiation of Cycle 2 by more than 14 days due to inadequate recovery of treatment-related hematological or nonhematologic toxicities.
- Any Grade 5 AE.
- Hematologic toxicity clearly unrelated to the underlying disease is defined as follows:
  - Nonfebrile Grade 4 neutropenia (absolute neutrophil count [ANC] $<0.5 \times 10^9$/L; ANC <500 cells/mm^3) lasting more than 7 consecutive days.
  - Febrile neutropenia: Grade ≥3 neutropenia (ANC $<1.0 \times 10^9$/L; ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as a body temperature >38.3°C or sustained temperature ≥38.0°C for more than 1 hour.
  - Grade 4 thrombocytopenia (platelets <25,000/mm^3) lasting more than 14 consecutive days.
  - Grade 3 thrombocytopenia (25,000 <platelets< 50,000/mm^3) with clinically significant bleeding.
- Any other Grade ≥4 hematologic toxicity with the exception of Grade 4 lymphopenia.
- Nonhematologic toxicity Grade ≥3 clearly unrelated to the underlying disease, **with the exception of:**
  - Asymptomatic laboratory changes (other than renal and hepatic laboratory values) that can be successfully supplemented (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline) within 72 hours.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Grade 3 nausea and/or emesis that can be controlled to Grade ≤3 in ≤2 days with the use of optimal antiemetics (defined as an antiemetic regimen that employs both a serotonin receptor subtype 3 antagonist and a corticosteroid given in standard doses and according to standard schedules).
- Grade 3 elevation in ALT, AST, and/or alkaline phosphatase that resolves to Grade ≤1 or baseline with supportive care within 7 days and is not associated with other clinically relevant consequences.
- Grade 3 IRR that resolves with appropriate clinical treatment, without recurrence of Grade 3 symptoms.
- Grade 3 fatigue lasting less than 72 hours.
- Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs (NSAIDs) within 7 days.
- Grade 3 diarrhea that can be controlled to Grade <3 in ≤3 days with appropriate treatment.
- Grade 3 rash and pruritis that respond to standard treatment and resolve or improve to Grade <3 in ≤72 hours.

8.5.1 Definition of DLT-Evaluable Patients

The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or patients who received a full dose of modakafusp alfa and at least 75% of the planned dose of the combination partners and completed evaluation for DLT in Cycle 1. The DLT-evaluable population will be used to determine the RP2D/MTD.

Patients who withdraw before completing the DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

8.5.2 Intrapatient Dose Escalation

Intrapatient dose escalation will be permitted only when patients have completed assessments for Cycle 1. Patients eligible for intrapatient escalation can also be changed to a different schedule once the conditions described above are met.

Patients who have tolerated treatment with modakafusp alfa well at the initially assigned dose may be allowed to increase their doses of modakafusp alfa in subsequent cycles of treatment following sponsor and investigator review of the available data. If the modakafusp alfa dose is to be increased, it may be increased to the highest dose that has been evaluated in the study and found to have an acceptable rate of DLT.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

8.6 Dose Modification Guidelines

8.6.1 Modakafusp Alfa and Combination Agent(s)

8.6.1.1 Criteria for Cycle 1 Day 1

For initiating Cycle 1 Day 1 of treatment (modakafusp alfa and combination agents), the patient must meet the following criteria:

- ANC ≥1000/mm^3 without ongoing G-CSF for at least 3 days before Cycle 1 Day 1.
- Platelet count must be ≥75,000/mm^3 without ongoing transfusion support for at least 1 week before Cycle 1 Day 1. Platelet transfusions can be given any time as clinically indicated but should not be given for only the purpose of meeting the treatment criterion for platelet count.
- Hb ≥8 g/dL. RBC transfusions can be given any time as clinically indicated.

The above-cited criteria apply to modakafusp alfa and the combination agent(s).

8.6.1.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle (Cycle 2 Day 1 and Beyond)

For a new cycle of treatment (modakafusp alfa and combination agents) to begin, the patient must meet the following criteria:

- ANC ≥1000/mm^3. G-CSF can be used to reach this level. G-CSF can be used to reach this level.
- Platelet count must be ≥50,000/mm^3. Platelet transfusion can be applied any time it is clinically indicated, but it should not be applied for only the purpose of meeting the treatment criterion for platelet count.

The aforementioned criteria apply to modakafusp alfa.

For therapy to resume, toxicity considered related to treatment with modakafusp alfa must have resolved to Grade ≤1 or baseline (Grade 2 for platelets) or to a level considered acceptable by the investigator. If the patient fails to meet the previously 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 retreatment criteria have been met.

If there is a delay of a subsequent cycle longer than 2 weeks because of a related AE, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor. Modakafusp alfa dosing may be continued at the previously established safe dose level or below.

8.6.1.3 Modakafusp Alfa

Dose modification guidelines for toxicities are described herein for modakafusp alfa 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).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Dose modifications are not permitted during Cycle 1 of therapy unless the patient experiences a DLT. DLTs are defined in Section 8.5. If a patient experiences a DLT during Cycle 1, the event will be counted toward the assessment of tolerable combination agent doses for the given cohort. Patients experiencing DLTs in Cycle 1 may continue in the study, but doses of lenalidomide, bortezomib, pomalidomide, daratumumab, or modakafusp alfa will be reduced as appropriate. Patients will be evaluated weekly for possible toxicities that may have occurred after the previous dose(s).

Toxicities are to be assessed according to the NCI CTCAE, Version 5.0. Toxicities should be attributed to a specific drug, if possible, to allow appropriate dose modification(s). Reduction of 1 agent and not the other is appropriate if toxicity is related primarily to 1 of the agents.

Before beginning the next cycle of treatment, refer to the dose modification guidelines below. Further clarification can be obtained in consultation with the sponsor clinician (or designee). If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the AE with the highest toxicity grade. The same dose modification guidelines will apply to subsequent cycles unless otherwise noted. Toxicities should be attributed to a specific study drug, if possible, to allow appropriate dose modification. If attribution to either drug is unclear, dose modification of modakafusp alfa should be considered first to allow full dosing of the combination agent if it is a reasonable approach for the particular situation.

Dose modification of the combination drugs should be in accordance with the respective drug's prescribing information. Alternative dose modifications may be recommended after discussion with the investigator and sponsor clinician/designee to maximize exposure of study treatment while protecting patient safety.

8.6.1.4 Criteria for Dose Interruption

All toxicities that occur during the study will be actively managed following the SOC unless otherwise specified in the protocol. Patients experiencing AEs attributed to modakafusp alfa may continue study treatment with the same dose, have modakafusp alfa treatment held, have the dose reduced, or 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 is recurrent.

Table 8.a and Table 8.b provide general dose modification recommendations for nonhematologic and hematologic toxicities, respectively. Table 8.c provides dose modification recommendations for bleeding TEAEs to mitigate the risk of fatal hemorrhagic events. If the modakafusp alfa dose 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, based on investigator assessment, are not clinically significant or drug related, continuation of therapy without dose modification is permissible upon discussion with the sponsor.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 8.a Dose Modification Recommendations for Modakafusp Alfa Nonhematological Toxicities

This table does not include guidance for management of bleeding TEAEs and IRRs. Refer to Table 8.c for the management of bleeding TEAEs and Table 8.e and Table 8.f for the management of IRRs.

Criteria	Action
Grade 1 and 2 AEs	No dose reductions or interruptions. Treat according to local practice.
Grade 3 AEs and asymptomatic Grade 4 laboratory AEs	Hold modakafusp alfa next infusion until resolution to Grade ≤1 or baseline, and then resume treatment. First occurrence: Resume treatment at either the same dose or reduced dose at the discretion of the investigator. Subsequent occurrence: Reduce modakafusp alfa by 1 dose level. 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.
Grade 4 AEs (except asymptomatic Grade 4 laboratory AEs)	Permanently withdraw the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor.

AE: adverse event; IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of bleeding TEAEs, which is found in Table 8.c or for the management of IRRs, which is found in Table 8.e, Table 8.f, and Section 8.7.1.1.

Table 8.b Dose Modification Recommendations for Modakafusp Alfa Hematological Toxicities

This table does not include guidance for management of bleeding TEAEs and IRRs. Refer to Table 8.c for the management of bleeding TEAEs and Table 8.e and Table 8.f for the management of IRRs.

Criteria	Action
Grade 1 and 2 AEs	No dose reductions or interruptions.
Grade 3 and 4 AEs	Hold modakafusp alfa next infusion until resolution to Grade ≤2 then resume treatment. Consider growth factors and/or transfusion according to local practice when clinically indicated. Please refer to Section 8.6.1 for the criteria of starting a new cycle of treatment. If the next cycle of modakafusp alfa is delayed for >14 days, study treatment should be discontinued unless the investigator considers that the patient will receive benefit continuing in the study.

AE: adverse event; IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of bleeding TEAEs, which is found in Table 8.c or for the management of IRRs, which is found in Table 8.e, Table 8.f, and Section 8.7.1.1.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 8.c Dose Modification Recommendations for Modakafusp Alfa Bleeding TEAEs

This table does not include guidance for management of IRRs. Refer to Table 8.e and Table 8.f for the management of IRRs.

Criteria	Action
Grade 1 and 2	No dose reductions or interruptions. Treat according to local practice.
Grade 3 without associated Grade 4 thrombocytopenia	Hold next infusion of modakafusp alfa until resolution to Grade ≤1 or baseline, and then resume treatment. Subsequent occurrence: Discontinue modakafusp alfa.
Grade 3 with associated Grade 4 thrombocytopenia	Discontinue modakafusp alfa.
Grade 4	Discontinue modakafusp alfa.

IRR: infusion-related reaction; TEAE: treatment-emergent adverse event.
This table does not include guidance for the management of IRRs, which is found in Table 8.e, Table 8.f, and Section 8.7.1.1.

8.6.1.5 Criteria for Dose Reduction

When a dose reduction occurs, the modakafusp alfa dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation (Table 8.d). 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.

Table 8.d Dose Reduction Levels for Modakafusp Alfa

Starting Dose	80 mg	120 mg	240 mg
First dose level reduction	60 mg	80 mg	120 mg
Second dose level reduction	Discontinue treatment	60 mg	80 mg
Third dose level reduction	NA	Discontinue treatment	60 mg

NA: not applicable.

8.6.1.6 Criteria for Discontinuation

Modakafusp alfa should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT for which the investigator considers that retreatment of the patient could be dangerous.

If the next cycle of modakafusp alfa is delayed for >14 days because of modakafusp alfa–related toxicities, study treatment should be discontinued unless the investigator considers that the patient will receive benefit continuing in the study. Patients will be evaluated approximately 30 days after the last dose of treatment (end-of-treatment [EOT] visit) or right before the start of subsequent systemic anticancer therapy to permit the detection of any delayed TEAEs.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Patients who discontinue modakafusp alfa because of TEAEs assessed by the investigator as related *only* to modakafusp alfa may continue the combination agent(s) at the discretion of the investigator and with agreement by the sponsor.

8.6.2 Combination Agents

Dose modifications (dose change, interruption, discontinuation) of the combination drugs should be done in accordance with the respective drug's local prescribing information. Alternative dose modifications may be recommended after discussion with the investigator and sponsor to maximize exposure of study treatment while protecting patient safety.

8.7 Management of Specific Adverse Reactions

8.7.1 Modakafusp alfa

8.7.1.1 Handling of IRRs Related to Modakafusp Alfa

An IRR is a reaction that develops during or shortly after administration of a drug. Signs and symptoms may include pruritus, urticaria, fever, rigors/chills, diaphoresis, bronchospasms, and cardiovascular collapse. In this study, IRRs are designated as AESIs.

It is mandatory that all patients receive premedication, including corticosteroids, before modakafusp alfa dosing (Section 8.1.1.1). Recommendations for premedications for combination therapies are detailed in Section 8.11.2. On days on which combination agents are given on the same visit day as modakafusp alfa, administer the modakafusp alfa-specific premedication only.

If a patient presents with an IRR at any dose level, the duration of the infusion of modakafusp alfa may be extended per investigator's discretion. Total time from modakafusp alfa dosing solution preparation until end of infusion must not exceed 7 hours. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See the IB and pharmacy manual for additional guidance.

Patients should be carefully observed during modakafusp alfa infusions and for at least 2 hours post infusion. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilators and medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside.

In case of an IRR, a serum sample for circulating biomarkers, a blood sample for flow cytometry, a blood sample for RNA, and a serum sample for immunogenicity (ADA/NAb) should be collected, if clinical management of the patient allows (as detailed in the SOEs in (Appendix A).

Patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion. All IRRs, including the signs and symptoms, will be reported in the eCRF per completion guidelines.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner.

Grade 1 and 2 IRRs

The recommendations for managing Grade 1 and Grade 2 IRRs are presented in Table 8.e.

Table 8.e Recommendations for Managing Grade 1 and Grade 2 IRRs

IRR	Action
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, infusion may be restarted at the investigator's discretion. On restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
Grade 2 or higher event of laryngeal edema, or Grade 2 or higher event of bronchospasm that does not respond to systemic therapy.	Patient must be withdrawn from treatment if the event does not resolve within 6 hours from onset.

IRR: infusion-related reaction.

Grade 3 or Higher IRRs

The recommendations for managing Grade ≥3 IRRs are presented in Table 8.f.

Table 8.f Recommendations for Managing Grade ≥3 IRRs

IRR	Action
Any Grade 4 event:	Patient must be withdrawn from treatment.
Grade 3 bronchospasm or laryngeal edema:	Patient must be withdrawn from treatment.
Grade 3 events other than bronchospasm or laryngeal edema:	Infusion must be stopped, and the patient must be observed carefully until resolution of the IRR.
If the intensity of the IRR remains at Grade 3 after 2 hours:	Patient must be withdrawn from treatment.
If the intensity of the IRR decreases to Grades 1 or 2:	Infusion may be restarted at the investigator's discretion. Within 2 hours of restart, the infusion rate should be half that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
If the intensity of the IRR returns to Grade 3:	The procedure described above may be repeated after restart of the infusion at the investigator's discretion.
If the intensity of the IRR increases to Grade 3 for a third time:	Patient must be withdrawn from treatment.

IRR: infusion-related reaction.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

8.7.1.2 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 infusions to be postponed or to be permanently discontinued. If at any time the platelet count is less than 10×10^9/L, after initiation of modakafusp alfa treatment, the patient should be withdrawn from modakafusp alfa treatment unless clinical benefit is observed and the investigator considers that thrombocytopenia can be managed, including with dose modifications. Dose modification for bleeding TEAEs should follow the recommendations included in Table 8.c. The investigator can consider the usage of corticosteroids, IVIG, or thrombopoietin agonists in selected cases depending on severity, duration, transfusion requirements, and additional risk factors for bleeding and based on the suspected underlying mechanism. Platelet transfusion and daily monitoring of platelet counts are recommended.

8.7.1.3 Prophylaxis Against Risk of Infection

Patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Prophylactic antiviral therapy such as acyclovir or valacyclovir should be initiated as clinically indicated.

8.7.2 Combination Agents

Please refer to the product labels for lenalidomide, pomalidomide, bortezomib and daratumumab for the management of product related clinical events.

On days when both daratumumab SC and modakafusp alfa are administered, please refer to product label for daratumumab SC for the management of IRR events when they occur after daratumumab SC administration and before modakafusp alfa administration.

8.8 Precautions and Restrictions

8.8.1 Contraception and Pregnancy Avoidance Procedures

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

Adherence to the prescribing information and any guidelines for treatment-specific pregnancy prevention programs (eg, REMS or Pregnancy Prevention Program for lenalidomide or pomalidomide), if applicable, is mandatory, as appropriate in the country.

Patients with a uterus and ovary(ies) must meet 1 of the following criteria:

- Postmenopausal for at least 2 years before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential:

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

- Agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Table 8.g) at the same time, from the time of signing of the ICF through 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate an egg or eggs (ova) or breastfeed a baby during the study through 7 days after the last dose of modakafusp alfa or through the period defined by the combination agent's label, whichever is longer.

Patients with a uterus and ovary(ies) must adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines. Specifically, lenalidomide and pomalidomide are similar to thalidomide and may cause severe life-threatening birth defects. Adherence to guidelines for any treatment-specific pregnancy prevention program, (eg, REMS or Pregnancy Prevention Program for lenalidomide or pomalidomide), if applicable, is mandatory, as appropriate in the country.

Patients with testis(es), even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception (see Table 8.g) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Patients with testis(es), even if surgically sterilized (ie, status postvasectomy), must:

- Agree not to donate sperm during the study and for 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, whichever is longer.
- Also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Table 8.g Highly Effective and Effective Methods of Contraception

Highly Effective Methods	Additional Effective (Barrier) Methods
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal	Male or female condom with or without spermicide (female and male condoms should not be used together)
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable • Implantable	
Intrauterine device	Cap, diaphragm, or sponge with spermicide
Intrauterine hormone-releasing system	
Bilateral tubal occlusion	
Vasectomized partner	
Sexual abstinence	

8.8.2 Pregnancy

Any participant who is found to be pregnant during the study should be withdrawn and modakafusp alfa should be immediately discontinued. In addition, any pregnancies in the partner of a study participant during the study should also be recorded, following authorization from the study participant's partner.

If a participant agrees to their primary care physician being informed, the investigator should notify the primary care physician that the participant was participating in a clinical study at the time of the pregnancy and provide details of the study drug the subject received.

All pregnancies, including those in partners of study participants, will be followed to final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

8.9 Blinding

This is an open-label study.

8.10 Description of Investigational Agents

Modakafusp alfa and combination agents used in this study are described in Sections 4.2 and 4.3.

8.10.1 Packaging and Labeling

Any sponsor-provided drugs will be labeled according to the current ICH guidelines on GCP and Good Manufacturing Practices and will include any locally required statements.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

8.11 Clinical Study Storage, Handling, and Accountability

8.11.1 Modakafusp Alfa

Modakafusp alfa must be stored according to the manufacturer's stipulation in a dry place at 2˚C to 8˚C (36˚F-46˚F).

Any comparators (Section 8.11.2) provided by the sponsor must be stored in compliance with labeled storage conditions.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all modakafusp alfa received and that any discrepancies are reported and resolved as outlined in the pharmacy manual. Each site shipment will include a packing slip listing the contents of the shipment, or any applicable forms.

The investigator is responsible for ensuring that deliveries of modakafusp alfa and other study materials from sponsor are correctly received, recorded, 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.

Only subjects enrolled in the study may receive modakafusp alfa and only authorized staff at the investigational center may supply or administer modakafusp alfa. All modakafusp alfa must be stored in a secure, environmentally controlled, and monitored (manual or automated) in accordance with labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

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

A record of modakafusp alfa accountability (ie, modakafusp alfa and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused modakafusp alfa will be disposed of, retained, or returned to the sponsor or designee.

Further guidance and information are provided in the pharmacy manual.

8.11.2 Combination Agents

All the combination agents (lenalidomide, pomalidomide, bortezomib, daratumumab) should be stored in accordance with the instructions provided in the manufacturer's product label. Additional details are provided in the respective package insert of the combination agent.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

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 other vendors such as the contract research organization (CRO) may be found in the ISF.

For 24-hour contact information, please refer to the ISF.

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/IEC.

9.3 Administrative Procedures

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

Sites will make every effort to see patients in the clinic to complete all study-specified assessments as outlined in the SOE.

In unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) public health emergency, exceptions can be made for alternative methods for conducting patient visits and performing laboratory and imaging assessments as detailed below. Remote visits and telemedicine must comply with national and local laws and regulations. Such instances will be documented in the study records and eCRF, if applicable, and the sponsor will be informed.

9.4 Informed Consent

Each patient must provide written or electronic informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care. For further details, please see Section 15.2.

Patients consenting electronically (eConsent), if available, will electronically sign consent forms. Paper consent forms will be used instead if required by local regulations. eConsent provides the same information as written consent forms, but in an electronic format that may include multimedia components. eConsent does not replace the important discussion between the study participant and site staff or investigator. Regardless of the consent format, the investigational site is responsible for the consenting process.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.5 Screening

Eligibility criteria and associated screening study assessments must be confirmed during the screening period; this must take place after a patient has provided informed consent but before receiving study drug.

Rescreening is permitted if in the opinion of the investigator, and upon consultation with the sponsor, a patient might meet all the eligibility criteria with the cause(s) of previous screening failure being resolved. The eligibility criteria for rescreening are the same as for initial screening.

9.6 Treatment Group Assignment

Patient will be assigned into a treatment regimen in a nonrandomized manner based upon the recruitment status of the available cohort as communicated by the sponsor and defined in the cohort management plan.

9.7 Study Procedures

9.7.1 Patient Demographics

The date of birth (outside European Economic Area) or age (European Economic Area), race, ethnicity (optional depending on country), and sex of the patient are to be recorded during screening, as permitted by local regulations.

9.7.2 Medical History

During the screening period, a complete medical history will be compiled for each patient. This includes initial diagnosis date, MM staging at initial diagnosis using International Staging System. Known cytogenetic alterations should be also collected, as well as prior treatment regimens, with each treatment duration (start and stop dates), and the best response obtained with each of them. Refractoriness to previous treatments should be collected following IMWG criteria. For patients who have received previous anti-CD38 treatment, the worst grade of IRR should be recorded. In addition, concomitant medications will be recorded.

9.7.3 Physical Examination

A complete physical examination will be completed per SOC at the times specified in the SOE (Appendix A). Physical examinations after the screening visit exam may be symptom directed.

If an investigator considers it safe and appropriate for a subject to miss a protocol-specified physical examination for COVID-19–related reasons, the study site physician or other qualified site staff will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) to assess subject safety and overall clinical status with a plan for in-person evaluation if signs and symptoms warrant. Such instances will be documented in the study records and eCRF if applicable, and the sponsor will be informed.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.7.4 Height and Weight

Height will be measured during the screening visit only. Weight will be measured at the times specified in Appendix A.

9.7.5 Vital Signs

Vital signs include temperature, pulse, respiratory rate, and oxygen saturation. They include also supine or seated measurements of diastolic and systolic blood pressure (BP) (after 3 to 5 minutes in this position; all measurements should be performed in the same initial position), heart rate, and body temperature. They will be measured at the times specified in Appendix A.

BP will be measured every 30 minutes (±5 minutes) during the first 4 infusions, at the end of all infusions, and at any moment the patient complains of symptoms consistent with an IRR. If the patient experiences hypotension (with or without symptoms), intensive BP monitoring according to local practice should be instituted. The patient cannot be released from the site until BP blood pressure has returned to Grade 1 or baseline for at least 1 hour. During all infusions and for at least 2 hours postdose, patients must be observed.

Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the eCRF as an AE and monitored as described in Section 10.0.

9.7.6 Pregnancy Testing

A participant of childbearing potential is defined as a participant with a uterus and ovary(ies) 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).

1) Screening/baseline: Participants of childbearing potential must have 2 negative pregnancy test results before starting study drug.
    - A urine or serum pregnancy test will be required during screening (within 10-14 days before start of study drug); this test must be negative.
    - A urine or serum pregnancy test must be performed at baseline (within 24 hours before the start of study drug). The results from these tests must be available and negative before the first dose of study drug is administered
2) On-treatment: During the study, participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle during treatment prior to dosing. If a menstrual period is delayed, absence of pregnancy in participants of childbearing potential must be confirmed by a negative urine or serum pregnancy test result.
    - For participants of childbearing potential in treatment arms with lenalidomide or pomalidomide, a pregnancy test is required weekly during the first 28 days of this study,

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

and a pregnancy test is required every 28 days if menstrual cycles are regular or every 14 days if menstrual cycles are irregular.

- Pregnancy tests may also be repeated during the study as per request of IRB or if required by local regulations.

3) EOT: At EOT, a urine or serum pregnancy test is required in participants of childbearing potential.

9.7.7 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures (including any transfusion) completed by the patient will recorded in the eCRF from signing of the ICF through 30 (+10) days after the last dose of treatment or the start of subsequent systemic anticancer therapy, whichever occurs first. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication(s) will be recorded. See Sections 8.2 and 8.3 regarding medications and therapies that are prohibited or allowed during the study.

9.7.8 AE Monitoring

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

9.7.9 ECOG Performance Status

ECOG performance status (Appendix H) will be evaluated and recorded as specified in the SOE (Appendix A).

9.7.10 Enrollment

Procedures for completing enrollment information are described in the Interactive Response Technology Systems User Guide.

9.7.11 12-Lead ECG

A 12-lead ECG will be administered at the time points specified in Appendix A. A qualified person will interpret the ECG locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator.

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 10.3.

9.7.12 Pulmonary Function Testing

A pulmonary function test (spirometry) will be administered during screening in treatment arms with daratumumab (Arm D). A qualified person will interpret the testing locally.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Spirometry will measure:

- FVC (forced vital capacity; maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration).
- FEV_1 (volume of air expressed in liters exhaled during the first second of performance of the FVC).

9.7.13 Patient Cards

9.7.13.1 PO Combination Agents Diary Card

Patients will be provided a diary card or equivalent on which the date of PO combination agents (lenalidomide, pomalidomide) administration and missed doses will be recorded. Complete instructions are on the diary card. The diary card will be reviewed by the study site per the SOE (Appendix A). If extenuating circumstances prevent a patient from attending the study site (eg, the COVID-19 pandemic), dosing diary cards should be returned at the next available on-site clinic visit.

9.7.13.2 Subject Identification Card

Patients will be provided a subject identification card that includes emergency medical contact information regarding their participation in this study. Patients should carry this card with them at all times and must provide this card to healthcare providers before blood transfusion.

9.7.14 Clinical Laboratory Procedures and Assessments

Clinical laboratory evaluations will be performed locally as indicated in each section. Local hematology and chemistry laboratory results should be used for dosing decisions.

In extenuating circumstances, such as during the COVID-19 public health emergency, laboratories closer to a patient's home may be utilized for local clinical laboratory assessments provided that pertinent laboratory information, including normal reference ranges, are provided to the sponsor or designee.

Not all collections are applicable to all cohorts or patients within a cohort. [redacted]

9.7.14.1 Clinical Laboratory Tests

Blood samples for analysis of the clinical chemistry and hematological parameters and urine samples for analysis of the urine parameters will be obtained as specified in Appendix A. They will be performed locally.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Hematology

Hematology will consist of the following tests:

Hematocrit	Leukocytes with differential [a]
Hemoglobin	Neutrophils (ANC)
Platelet (count)	Schistocytes [b]

ANC: absolute neutrophil count.

[a] Differential to include basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

[b] Only for Arm 3 at timepoints defined in the schedules of events.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Standard C-reactive protein
Alkaline phosphatase (ALP)	Chloride
Alanine aminotransferase (ALT)	Glucose (nonfasting)
Aspartate aminotransferase (AST)	Lactate dehydrogenase (LDH)
Bilirubin (total)	Magnesium
Blood urea nitrogen (BUN) or urea	Phosphate
Calcium	Potassium
Bicarbonate (HCO_3^-) or carbon dioxide (CO_2)	Sodium
Creatinine	Urate
Ferritin [a]	

[a] Only for Arm 3 at time points defined in the schedules of events.

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

Estimated creatinine clearance

$$= [(1–0.3 \times \text{Age}) \times \text{Mass (kg)}] / [72 \times \text{serum creatinine (mg/dL)}].$$

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

For transgender patients, use the sex at birth for patients not using hormone therapy or for patients who have used hormone therapy for <6 months; use the current gender for patients who have used hormone therapy for ≥6 months.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Urinalysis

Urinalysis will consist of the following tests.

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

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC/high-power field, white blood cell/high-power field, casts, bacteria, and crystals.

Other

Hepatitis B serology (HBsAg, HBcAb, HBsAb)	Serum β_2 microglobulin
HBV DNA test (polymerase chain reaction)	Thyroid function tests (TSH, free T4)
ABO blood group and Rh factor, direct and indirect antiglobulin tests (direct and indirect Coombs tests)	
HBsAg: hepatitis B surface antigen; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBV: hepatitis B virus; T4: thyroxine; TSH: thyroid stimulating hormone/thyrotropin.	

Hepatitis B serology (HBsAg, hepatitis B core antibody, hepatitis B surface antibody) will be performed at screening. Patients with resolved hepatitis B infection (ie, patients who are HBsAg negative but positive for antibodies to anti–hepatitis B core antibody and/or antibodies to anti-HBs) must be screened using real-time PCR measurement of HBV DNA levels. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

9.8 Study Compliance

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

9.9 Disease Assessment

Disease assessments will be performed locally unless otherwise specified as detailed in the SOE (Appendix A) and evaluated according to IMWG criteria (Appendix G).

In extenuating circumstances, such as during the COVID-19 public health emergency, patients may use an alternative site for imaging with prior notification to the sponsor or designee.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Serum and urine response assessments will be performed as indicated in the SOE (Appendix A). Imaging tests for qualifying patients are to be performed as indicated in the SOE (Appendix A). Investigators will assess disease response/status. Response and relapse categories are described in Appendix G.

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

Please note that to determine a response of sCR, bone marrow immunohistochemistry or immunofluorescence for the κ:λ 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 laboratories may be used to confirm PD.

The disease assessments in Sections 9.9.1 through 9.9.7 will be performed as indicated in the SOE (Appendix A).

9.9.1 Extramedullary Disease Imaging

Patients with previously documented extramedullary disease or with suspicion of extramedullary progression will have a positron emission tomography–computed tomography (PET-CT) scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan performed at screening (adequate imaging tests performed within 5 weeks of the planned first dose of study drug can be used as baseline and do not need to be repeated as part of screening) as needed for evaluation of disease. If extramedullary disease is documented at screening, repeat imaging using the same modality every 12 weeks (± 7 days) until a plateau or CR is reached, or as clinically indicated, and then at suspected progression (Hillengass et al. 2019). A plasmacytoma is considered measurable if the longest diameter is at least 1 cm and the product of the cross diameters is at least 1 cm^2. Plasmacytomas of lesser size will be considered nonmeasurable. The requirement for bidirectional measurements applies only to plasmacytomas. Imaging tests for patients with extramedullary disease should be performed if new symptoms suggest PD.

All follow-up scans should use the same imaging modality as used at screening.

Images will be analyzed locally and reports will be maintained with the patient's record for retrieval during monitoring visits. Deidentified copies of all imaging scans (including those from screening and any unscheduled scans) may be collected and transferred to the sponsor or designee for storage as needed.

9.9.2 Bone Imaging

Whole body bone imaging will be performed at screening (adequate imaging tests performed within 5 weeks of the planned first dose of study drug can be used as baseline and do not need to be repeated as part of screening). Whole body bone imaging can be done using either low-dose whole-body CT scan, PET-CT scan, or whole-body MRI (Hillengass et al. 2019). Low-dose

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

whole-body CT is recommended over conventional skeletal survey (series of radiographs) for the evaluation of MM bone disease. Therefore, conventional skeletal survey should be used only when whole-body CT or other novel imaging methods are not available.

If symptoms or signs suggest increased or new bone lesions, either whole body bone imaging or localized imaging of symptomatic sites may be performed. Additional assessments for bone disease, either whole body bone imaging or localized imaging of symptomatic sites, can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) during the study and at the EOT visit.

The same assessment modality should be used throughout the study.

Patients with no bone disease or only bone disease at baseline do not need to repeat imaging periodically unless clinically indicated.

Images will be analyzed locally and reports will be maintained with the patient record for retrieval during monitoring visits. Deidentified copies of all imaging scans (including those from screening and any unscheduled scans) may be collected and transferred to the sponsor or designee for storage as needed.

9.9.3 Quantification of Igs

A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained as specified in Appendix A. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA). Analysis of Ig will be performed locally.

9.9.4 Quantification of M-Protein in Serum and Urine

A blood and 24-hour urine sample will be obtained as specified in the SOE (Appendix A). Urine collection and testing will be repeated at the times specified only for patients with a baseline urine M-protein m≥200 mg/24 hours.

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

9.9.5 Serum FLC Assay

Blood samples will be obtained as specified in Appendix A for the serum FLC assay (including quantification of κ and λ chains and the κ:λ ratio). Blood samples will be analyzed locally.

9.9.6 Immunofixation of Serum and Urine

Serum and urine samples will be obtained as specified in the SOE (Appendix A) at screening and to confirm a CR. Immunofixation of serum and/or urine may be omitted at screening if a previous local laboratory report for the SPEP and/or UPEP states that the observed monoclonal spike is consistent with one previously characterized by immunofixation and specifies the heavy chain and light chain previously identified. Immunofixation testing will be performed locally.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.9.7 BMA

Bone marrow samples will be collected as detailed below and in Appendix B.

9.9.7.1 Local Laboratory Evaluations

9.9.7.1.1 Disease Assessment

A BMA will be obtained at screening for disease assessment and at any time during treatment to assess CR or to investigate suspected PD if it is in accordance with standard local practice. This evaluation will be performed locally. Clonality for sCR should be established by showing κλ light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence in bone marrow (Appendix B).

9.9.7.1.2 Cytogenetics

Cytogenetic evaluation will be analyzed locally, according to local standards, if the site has the capability to perform analysis. These analyses should be performed at screening using fluorescence in situ hybridization and/or conventional cytogenetics (karyotype).

Cytogenetic results from samples taken within 5 weeks before the first dose are acceptable.

9.9.7.2 Central Laboratory Evaluations

9.9.7.2.1 BMA for MRD Assessment

For patients enrolled in MM maintenance (Group 1), a BMA sample to evaluate MRD status should be collected at screening, 6 months, 1 year, and 2 years after the start of treatment and shipped in accordance with the procedures outlined in the laboratory manual. For patients to meet inclusion criteria for the MM maintenance arm, they must have a post-ASCT MRD positive assessment at a threshold of 10^{-5}. If local methodologies do not meet the sensitivity threshold requirements or if the patient did not have a prior assessment, the sample collected for central analysis of MRD at screening can be used to confirm eligibility.

For patients enrolled in the RRMM doublet and RRMM triplet groups, a BMA for MRD sample should be collected at the same time as the BMA/biopsy procedure is performed for local disease assessment purposes when a CR is suspected on laboratory values, as per routine clinical practice (Appendix B). Additional BMAs for MRD assessments will be collected at 6 months, 1 year, and 2 years following CR confirmation. The BMA for MRD samples should be collected and shipped in accordance with the procedures outlined in the laboratory manual.

9.9.7.2.2 Fresh BMA Sample

For all RRMM patients, a BMA (first or second pull preferred) will be obtained at screening and optionally at relapse (for patients who have responded to treatment) [redacted]. BMA samples should be collected and shipped in accordance with the procedures outlined in the laboratory manual.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.10 Biomarker, PK, Pharmacodynamic, and Pharmacogenomics, Samples

9.10.1 Primary Specimen Collection for PK, Pharmacodynamic, and Biomarker Assessments

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in the SOE (Appendix A) for serum concentration measurements of modakafusp alfa and biomarker assessments (with the exception of bone marrow biopsy and BMA). Other samples will be collected as detailed in the SOE. The primary specimen collection is presented in Table 9.a.

[redacted]

Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Serum sample for modakafusp PK	Blood	Serum	Modakafusp alfa concentrations	Mandatory
Bone marrow aspirate for MRD	BMA		Biomarker measurements	Mandatory
Fresh bone marrow aspirate sample	BMA	DNA RNA Plasma Cells	Biomarker measurements	Mandatory
Serum sample for immunogenicity and NAb	Blood	Serum	Immunogenicity (ADA and NAb) against modakafusp alfa	Mandatory
Blood sample for flow cytometry	Blood		Biomarker measurements	Mandatory
Serum sample for circulating biomarkers	Blood	Serum	Biomarker measurements	Mandatory
Blood sample for RNA	Blood	RNA	Biomarker measurements	Mandatory
[redacted]				

ADA: antidrug antibody; MRD: minimal/measurable residual disease; NAb: neutralizing antibody; PK: pharmacokinetic(s).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.10.2 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual. Serum samples for PK will be collected at the time points specified in Appendix C.

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 sampling scheme is considered necessary to better characterize the PK of modakafusp alfa.

9.10.3 [redacted]

[redacted]

9.10.3.1 [redacted]

[redacted]

9.10.3.2 [redacted]

[redacted]

Property of Takeda. For non-commercial use only. Subject to applicable Terms of Use

[redacted]

9.10.4 [redacted]

9.10.4.1 [redacted]

[redacted]

9.10.5 Immunogenicity Sample Collection

Serum samples prepared from blood for assessment of ADA and neutralizing ability (Nab) will be collected at the time points specified in the SOE (Appendix A) and as outlined in the laboratory manual. Samples must be collected before study drug is administered on a dosing day, and it is strongly suggested that samples be obtained at unscheduled visits for a subject who experiences Grade ≥2 hypersensitivity/IRR (Section 8.7.1.1).

If a patient experiences an IRR, blood samples should be collected for central evaluation of immunogenicity as clinical management of the patient permits (Section 8.7.1.1).

Property of Takeda. For Non-commercial use only and subject to applicable Terms of Use

Confirmed positive ADA samples will be assayed for titer and domain specificity characterization and further assessed for NAb. These samples will be analyzed at a central laboratory.

ADA-confirmed positive samples will be further assessed for NAb. These samples will be analyzed at a central laboratory.

9.11 Criteria for Discontinuation or Withdrawal of a Subject

Study drug must be permanently discontinued if the 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.

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

- SAE or AE.
- CR (after discussion with sponsor).
- Protocol deviation (after discussion with sponsor).
- PD (if the investigator considers that treatment after PD is in the patient's best interest, it can be approved after consultation with the sponsor).
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by subject.
- A participant has a confirmed pregnancy.
- Lost to follow-up.
- Other.

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

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Completed study.
- Transfer of patient to a long-term safety study, single-patient investigational new drug application, or similar program.
- Death.
- Other.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

9.12 Procedures for Discontinuation or Withdrawal of a Subject

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

Patients who discontinue study drug for reasons other than PD before completing the full treatment course will remain in the study for posttreatment assessments as outlined in the SOE (Appendix A) until PD or withdrawal of consent.

9.13 Subject Replacement

Patients who have not received at least 75% of the combination agent dosing during Cycle 1 for reasons other than a DLT will be replaced.

9.14 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they discontinued study drug for any reason outlined in Section 9.11. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.

9.15 Posttreatment Follow-up Assessments

Patients who stop treatment for any reason other than PD will continue to have PFS visits. The PFS visits should occur Q4W from EOT until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first. Imaging tests for patients with extramedullary disease should be performed every 12 weeks or if new symptoms suggest PD.

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

NOTE: Treatment-related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.1.4 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

AE and SAE rates and frequency will be categorized by toxicity grades (severity) will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and the NCI CTCAE Version 5.0.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has provided informe(e)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 AESIs

An AESI, serious or nonserious, is an AE of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to Takeda sponsor is appropriate. Such events may require further investigation to characterize and understand them. In modakafusp alfa studies, IRRs are designated as AESIs. Instructions regarding how and when AESIs should be reported to the sponsor are provided in Section 10.2.1.

10.1.4 SAEs

SAE means any untoward medical occurrence that at any dose:

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

Property of Takeda. For noncommercial use only and subject to the applicable Terms of Use

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

- In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, effective 27 November 2017 (ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Referen ce_8.5x11.pdf).

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Reporting and Recording AEs and SAEs

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

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

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

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

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

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

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 5.0. The criteria are provided in the ISF.

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?

10.2.1 Reporting AESIs

In modakafusp alfa studies, IRRs are designated as AESIs. An IRR can develop during or shortly after administration of a drug.

Patients will be advised to promptly report signs and symptoms that may indicate IRRs, including fever, chills, dizziness, nausea, vomiting, flushing, cough, headache, and rash during or soon after end of infusion. Signs and symptoms may also include pruritus, urticaria, rigors, diaphoresis, bronchospasms, and cardiovascular collapse.

Management guidelines are detailed in Section 8.7.1.1. When reporting IRRs in the eCRF, the signs and symptoms should be recorded and should be marked as an IRR. Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner irrespective of the event's causal relationship.

10.3 Monitoring AEs and Periods of Observation

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

- AEs will be reported from the signing of informed (e)consent through 30 days after administration of the last dose of study drug or start of subsequent anticancer therapy, whichever occurs first and recorded in the eCRFs.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed (e)consent through 30 days after administration of the last dose of study drug, even if the patient starts nonprotocol therapy and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product, device, or combination product. Individuals who identify a potential product complaint situation should immediately report this via the contact information provided in the ISF.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not.

Individuals who identify a potential medication error (including overdose) situation should immediately report this via the contact information provided in the ISF.

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs 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 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 products administration or in the overall conduct of the trial. The investigational sites also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEE

No committees will be used in this study.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each subject who signs €informed (e)consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will arrange training for 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 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 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. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the 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 documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, 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 subject's chart to ensure long-term legibility.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Furthermore, ICH E6 Section 4.9.5 requires investigators 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 and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

13.1.1.1 Safety Analysis Set

The safety analysis set will include all patients who have received at least 1 dose, even if incomplete, of any study drug.

13.1.1.2 PK Analysis Set

Patients from the safety analysis set with sufficient dosing and PK data to reliably report 1 or more PK concentration will be used for PK analyses.

13.1.1.3 DLT-Evaluable Analysis Set

The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or patients who received a full dose of modakafusp alfa and at least 75% of the planned dose of the combination partners and completed evaluation for DLT in Cycle 1. The DLT-evaluable population will be used to determine the RP2D/MTD.

13.1.1.4 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 postbaseline efficacy evaluation.

13.1.1.5 Immunogenicity-Evaluable Analysis Set

Analysis will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

13.1.1.6 MRD Analysis Set

The MRD-evaluable analysis set for Group 1 (MM maintenance) will be all patients who are MRD+ on study entry, as determined by the required central analysis for MRD at screening. The MRD-evaluable analysis set for Group 2 (RRMM doublets) and Group 3 (RRMM triplets) will be a subset of the safety analysis set including all patients who are in CR and have at least 1 evaluable postbaseline MRD assessment.

13.1.2 Analysis of Demography and Other Baseline Characteristics

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

13.1.3 Efficacy Analysis

13.1.3.1 Group 1: MM Maintenance

No primary efficacy endpoint is included. Secondary efficacy endpoints include PFS; ORR (local assessment); DOR; rate of MRD[-] at a threshold of 10^{-5} in patients at 6 months, 1 year, and 2 years after the start of treatment; and duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-].

PFS is defined as the time from the date on which the first dose of study drug is administered to the date of first documentation of confirmed PD or death due to any cause, whichever occurs first. PD will be determined by IMWG criteria. Patients without documentation of PD or death will be censored at the date of last response assessment.

DOR is defined as time from the date of first documentation of a confirmed PR or better to the date of first documentation of PD or death due to any cause. DOR will be calculated for responders only (PR or better). Responders without documentation of PD or death will be censored at the date of last response assessment that is stable disease or better.

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

Rate of MRD[-] is defined as the proportion of patients who have achieved MRD[-] status.

Duration of MRD[-] is defined as the time from the date of first documentation of MRD[-] to the first documentation of MRD positivity or confirmed PD or death due to any cause, whichever occurs first. Patients without documentation of MRD positivity or confirmed PD will be censored at the date they were last known to be MRD[-].

PFS will be analyzed using the safety analysis set and summarized using the Kaplan-Meier (KM) method. ORR will be analyzed using the response-evaluable analysis set, and the rate of MRD[-] will be analyzed on the basis of the MRD analysis set. Both endpoints will be summarized with

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

2-sided 95% exact binomial CIs. Duration of MRD[-] will be analyzed in patients achieving MRD[-] by using the KM method.

13.1.3.2 Group 2 and Group 3: RRMM Doublets and Triplets

No primary efficacy endpoints are included. Secondary endpoints include OS, ORR, PFS, TTP, TTNT, DOR, DCR, EFS, TTR, rate of MRD[-] CR at a threshold of 10^{-5} with CR assessed by the investigator, rate of MRD[-] at a threshold of 10^{-5}, and duration of MRD[-] at a threshold of 10^{-5} in patients achieving MRD[-].

DOR, ORR, PFS, rate of MRD[-], and duration of MRD[-] are defined the same as previously described for maintenance.

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

TTP is defined as the time from the date of the first dose administration to the date of the first documentation of confirmed PD as defined by IMWG criteria. Patients without documentation of progression will be censored at the date of last response assessment.

TTNT is defined as the time from the date of first dose administration to the date of the first dose initiation of the next line of antineoplastic therapy, for any reason. Patients who have not started a next line of therapy will be censored at the date last known to be alive before subsequent anticancer therapy.

DCR is defined as the proportion of patients with a confirmed response sCR, CR, VGPR, PR, minimal response, or stable disease based on investigator's disease assessment per IMWG criteria.

EFS is defined as the time from the date on which the first dose of study drug is administered to the date of the first documentation of an event that may include confirmed PD, discontinuation of a treatment for an AE (related or not related), or death due to any cause, whichever occurs first. PD will be determined by IMWG criteria. Patients without documentation of PD, discontinuation of treatment, or death will be censored at the date of their last response assessment.

TTR is defined as the time from the date of the first dose administration to the date of the first documentation of objective confirmed response as defined by IMWG criteria.

ORR and DCR will be analyzed using the response-evaluable analysis set and summarized descriptively with 2-sided 95% exact binomial CIs.

DOR and TTR will be analyzed for responders only. DOR will be summarized using KM method and descriptive summary will be provided for TTR as a continuous variable.

OS, PFS, EFS, TTP, and TTNT will be analyzed using the safety analysis set and summarized descriptively using KM method for safety analysis set.

Rate of MRD[-] CR is defined as the proportion of patients who have achieved MRD[-] CR status.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Rate of MRD[-] CR will be analyzed for both the MRD-evaluable analysis set and the safety analysis set and summarized with 2-sided 95% exact binomial CIs. Rate of MRD[-] will be analyzed for the safety analysis set and summarized with 2-sided 95% exact binomial CIs. Duration of MRD[-] will be analyzed in patients achieving MRD[-] using the KM method.

13.1.4 PK Analysis

The PK of modakafusp alfa will be characterized in this study.

The PK data collected in this study are intended to contribute to future population PK and exposure-response analyses of modakafusp alfa. These population PK and exposure-response analyses may include data collected in other modakafusp alfa clinical single or combination studies. The analysis plan for the population PK and exposure-response analyses will be separately defined, and the results of these analyses will be reported separately.

13.1.5 Immunogenicity Analyses

The proportion of subjects with positive ADA (rate, titer and domain specificity) and NAb against modakafusp alfa in the study will be summarized. [redacted]

13.1.6 Safety Analysis

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

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

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

13.1.6.1 TEAEs

TEAE incidence rates and frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be tabulated according to the MedDRA and the NCI CTCAE Version 5.0. These data will be presented in the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.

Property of Takeda For non-commercial use only and subject to the applicable Terms of Use

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

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

13.1.6.2 Clinical Laboratory Evaluation

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

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

13.1.6.3 Vital Signs

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

13.1.6.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

Additional safety parameters may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of modakafusp alfa.

13.2 Interim Analysis and Criteria for Early Termination

Although no formal interim analysis is planned, investigators and sponsor representatives will review accruing data to determine dose escalation and number of patients per cohort in the treatment phase.

13.3 Determination of Sample Size

The BOIN design will be implemented to guide the dose escalation/de-escalation. The target toxicity rate for MTD is set to $\phi = 0.25$ for MM maintenance as well as RRMM doublets and $\phi = 0.33$ for RRMM triplets. Patients will be enrolled and treated in cohorts of size approximately 3. It is estimated that a total of approximately 120 DLT-evaluable patients will be enrolled: approximately 18 for MM maintenance (Arm 1), approximately 66 for RRMM doublet combinations, and approximately 36 for RRMM triplet combinations.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

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 study site 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 the sponsor's designee, including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, 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 trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of the primary study assessments.

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom [UK] MHRA [Medicines and Healthcare products Regulatory Agency], the PMDA [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 guarantees access for quality assurance auditors to all study documents as described in Section 14.1.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

15.0 ETHICAL ASPECTS OF THE STUDY

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

. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject 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 subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by 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/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

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

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

15.2 Subject Information, Informed (e)Consent, and Subject Authorization

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

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

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

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject is enrolled into the study. The subject or the subject'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 subject authorization (if applicable) at the time of consent and before the subject is enrolled into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

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

Subjects who consented and provided a pharmacogenomics sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. Sites must notify the sponsor of consent withdrawal.

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

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

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

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor 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, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

16.0 REFERENCES

Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021. Prescribing Information. Summit, NJ: Celgene Corporation.

Aletaha, D., Landewe, R., Karonitsch, T., Bathon, J., Boers, M., Bombardier, C., et al. 2008. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum,* 59(10), 1371-7.

Bauvois, B., Durant, L., Laboureau, J., Barthelemy, E., Rouillard, D., Boulla, G., et al. 1999. Upregulation of CD38 gene expression in leukemic B cells by interferon types I and II. *Journal of Interferon & Cytokine Research,* 19(9), 1059-66.

Bolognesi, A., Polito, L., Farini, V., Bortolotti, M., Tazzari, P. L., Ratta, M., et al. 2005. CD38 as a target of IB4 mAb carrying saporin-S6: design of an immunotoxin for ex vivo depletion of hematological CD38+ neoplasia. *Journal of Biological Regulators & Homeostatic Agents,* 19(3-4), 145-52.

Chapman, M. A., Lawrence, M. S., Keats, J. J., Cibulskis, K., Sougnez, C., Schinzel, A. C., et al. 2011. Initial genome sequencing and analysis of multiple myeloma. *Nature,* 471(7339), 467-72.

Chillemi, A., Zaccarello, G., Quarona, V., Ferracin, M., Ghimenti, C., Massaia, M., et al. 2013. Anti-CD38 antibody therapy: windows of opportunity yielded by the functional characteristics of the target molecule. *Molecular Medicine,* 19, 99-108.

Cook, J., Johnson, I., Higgins, A., Sidana, S., Warsame, R., Gonsalves, W., et al. 2021. Outcomes with different administration schedules of bortezomib in bortezomib, lenalidomide and dexamethasone (VRd) as first-line therapy in multiple myeloma. *Am J Hematol,* 96(3), 330-7.

Cowan, A. J., Allen, C., Barac, A., Basaleem, H., Bensenor, I., Curado, M. P., et al. 2018. Supplement to: Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. *JAMA Oncol,* 4(9), 1221-7.

Darzalex (daratumumab) injection for intravenous use 2021. Prescribing Information. Horsham, PA 19044: Janssen Biotech, Inc.

Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection for subcutaneous use 2021. Prescribing Information. Horsham, PA: Janssen Biotech, Inc.

Deaglio, S., Aydin, S., Vaisitti, T., Bergui, L. and Malavasi, F. 2008. CD38 at the junction between prognostic marker and therapeutic target. *Trends in Molecular Medicine,* 14(5), 210-8.

Deaglio, S., Mehta, K. and Malavasi, F. 2001. Human CD38: a (r)evolutionary story of enzymes and receptors. *Leuk Res,* 25(1), 1-12.

Funaro, A., Horenstein, A. L., Calosso, L., Morra, M., Tarocco, R. P., Franco, L., et al. 1996. Identification and characterization of an active soluble form of human CD38 in normal and pathological fluids. *International Immunology,* 8(11), 1643-50.

Funaro, A., Spagnoli, G. C., Ausiello, C. M., Alessio, M., Roggero, S., Delia, D., et al. 1990. Involvement of the multilineage CD38 molecule in a unique pathway of cell activation and proliferation. *Journal of Immunology,* 145(8), 2390-6.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Goldmacher, V. S., Bourret, L. A., Levine, B. A., Rasmussen, R. A., Pourshadi, M., Lambert, J. M., et al. 1994. Anti-CD38-blocked ricin: an immunotoxin for the treatment of multiple myeloma. *Blood,* 84(9), 3017-25.

Green, D. J., Orgun, N. N., Jones, J. C., Hylarides, M. D., Pagel, J. M., Hamlin, D. K., et al. 2014. A preclinical model of CD38-pretargeted radioimmunotherapy for plasma cell malignancies. *Cancer Research,* 74(4), 1179-89.

Grosicki, S., Simonova, M., Spicka, I., Pour, L., Kriachok, I., Gavriatopoulou, M., et al. 2020. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet,* 396(10262), 1563-73.

Hillengass, J., Usmani, S., Rajkumar, S. V., Durie, B. G. M., Mateos, M. V., Lonial, S., et al. 2019. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. *Lancet Oncol,* 20(6), e302-e12.

Holstein, S. A., Jung, S. H., Richardson, P. G., Hofmeister, C. C., Hurd, D. D., Hassoun, H., et al. 2017. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol,* 4(9), e431-e42.

Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., et al. 2016. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol,* 17(8), e328-46.

Kumar, S. K., Lee, J. H., Lahuerta, J. J., Morgan, G., Richardson, P. G., Crowley, J., et al. 2012. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia,* 26(1), 149-57.

Lacy, M. Q., Allred, J. B., Gertz, M. A., Hayman, S. R., Short, K. D., Buadi, F., et al. 2011. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood,* 118(11), 2970-5.

Lacy, M. Q., Hayman, S. R., Gertz, M. A., Dispenzieri, A., Buadi, F., Kumar, S., et al. 2009. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol,* 27(30), 5008-14.

Lesinski, G. B., Raig, E. T., Guenterberg, K., Brown, L., Go, M. R., Shah, N. N., et al. 2008. IFN-alpha and bortezomib overcome Bcl-2 and Mcl-1 overexpression in melanoma cells by stimulating the extrinsic pathway of apoptosis. *Cancer Res,* 68(20), 8351-60.

Lin, P., Owens, R., Tricot, G. and Wilson, C. S. 2004. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. *Am J Clin Pathol,* 121(4), 482-8.

Liu, S. and Yuan, Y. 2015. Bayesian optimal interval designs for phase I clinical trials. *J R Stat Soc Ser C Appl Stat,* 64(3), 507-23.

Markowitz, J., Luedke, E. A., Grignol, V. P., Hade, E. M., Paul, B. K., Mundy-Bosse, B. L., et al. 2014. A phase I trial of bortezomib and interferon-α-2b in metastatic melanoma. *J Immunother,* 37(1), 55-62.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Moreau, P., Kumar, S. K., San Miguel, J., Davies, F., Zamagni, E., Bahlis, N., et al. 2021. Treatment of relapsed and refractory multiple myeloma: recommendations from the international myeloma working group. *Lancet Oncol,* 22(3), e105-e18.

O'Donnell, E. K., Laubach, J. P., Yee, A. J., Chen, T., Huff, C. A., Basile, F. G., et al. 2018. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol,* 182(2), 222-30.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., et al. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol,* 5(6), 649-55.

Pomalyst (pomalidomide) Capsules 2020. Prescribing Information. Summit, NJ: Celgene Corporation.

Rajkumar, S. V. 2014. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. *Am J Hematol Oncol,* 89(10), 998-1009.

Rajkumar, S. V., Harousseau, J. L., Durie, B., Anderson, K. C., Dimopoulos, M., Kyle, R., et al. 2011. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood,* 117(18), 4691-5.

Rajkumar, S. V. and Kumar, S. 2016. Multiple Myeloma: Diagnosis and Treatment. *Mayo Clin Proc,* 91(1), 101-19.

Revlimid (lenalidomide) 2021. Summary of Product Characteristics. Utrecht, Netherlands: Celgene Distribution B.V.

Santonocito, A. M., Consoli, U., Bagnato, S., Milone, G., Palumbo, G. A., Di Raimondo, F., et al. 2004. Flow cytometric detection of aneuploid CD38(++) plasmacells and CD19(+) B-lymphocytes in bone marrow, peripheral blood and PBSC harvest in multiple myeloma patients. *Leukemia Research,* 28(5), 469-77.

Sarclisa (Isatuximab) 2020. Package Insert. Bridgewater, NJ: Sanofi-Aventis.

Velcade (bortezomib) for Injection 2019. Prescribing Information. Cambridge, MA: Millennium Pharmaceuticals, Inc.

Vogl, D. T., Kaufman, J. L., Holstein, S. A., Atrash, S., Nadeem, O., Janakiram, M., et al. 2021. Modakafusp alfa (TAK-573), an immunocytokine, shows clinical activity in patients with relapsed/refractory multiple myeloma; updated results from a first-in-human phase 1 study. Abstract No. 898. *Blood,* 138, 898-9.

Xpovio (selinexor) tablets for oral use 2021. Prescribing Information. Newton, MA: Karyopharm Therapeutics Inc.

Zhou, Y., Lin, R., Kuo, Y. W., Lee, J. J. and Yuan, Y. 2021. BOIN suite: A software platform to design and implement novel early-phase clinical trials. *JCO Clin Cancer Inform,* 5, 91-101.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

17.0 APPENDICES

17.1 Appendix A Schedules of Events

Appendix A Table 1 Group 1 Arm 1 MM Maintenance Modakafusp Alfa IV and Lenalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [b] and subject identification card issued	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
Height and weight [c]	X					X			
ECOG performance status	X					X			
12-lead ECG [d]	X	X		X		X		X	
Physical examination [e]	X	X		X		X		X	
Vital signs [f]	X	X		X		X		X	
Diary card [m]		X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.								

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 1 Group 1 Arm 1 MM Maintenance Modakafusp Alfa IV and Lenalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Dosing									
Modakafusp alfa infusion [g]		X				X			
Lenalidomide PO [h]		→ [a]	→ [a]	→ [a]	→ [a]	→ [a]	→ [a]	→ [a]	→ [a]
Imaging Assessments *(local)*									
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).							
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9).							
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule Section 9.9.							
Safety Laboratory Assessments *(local analysis)*									
Chemistry [q]	X	(X)	X	X	X	X	X	X	X
Hematology [r]	X	(X)	X	X	X	X	X	X	X
Thyroid function [s]	X								
Viral serologies [t]	X								
Urinalysis [u]	X								
Pregnancy test [v]	X	X	X	X	X	X			
ABO blood group and Rh factor; direct and indirect Coombs tests	X								

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 1 Group 1 Arm 1 MM Maintenance Modakafusp Alfa IV and Lenalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Disease Assessments									
Serum M-protein [w]	X	(X)		X		X		X	
24-hour urine M-protein [w, x]	X	(X)		(X)		(X)		(X)	
Serum FLC assay [w]	X	(X)		X		X		X	
Immunofixation - serum and urine [w, y]	(X)	(X)		X		X		X	
Quantification of Ig [w, z]	X	(X)				X			
Serum β_2 microglobulin	X								
BMA/biopsy	X	Refer to Appendix B							
Investigator assessment of disease response/ status						X			
Biologic Laboratory Assessments *(central analysis)*									
Serum sample for modakafusp alfa PK		Refer to Appendix C							
Blood sample for flow cytometry [g, aa]		X [bb]	X	X	X	X [bb]	X	X	X
Serum sample for circulating biomarkers [g]		X [ii]	X	X	X				
Serum sample for immunogenicity (ADA/NAb) [g, cc]		X		X		X		X	
[redacted]									
Blood sample for RNA [g]		X [ii]	X	X	X				

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 2 Group 1 Arm 1 MM Maintenance Modakafusp Alfa IV and Lenalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**				
Cycle Day	C3D1	C4D1	C5D1	C6D1	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Weight [c]	X	X	X	X	X
ECOG performance status	X	X	X	X	X
12-lead ECG [d]		X		X	X
Physical examination [e]	X	X	X	X	X
Vital signs [f]	X	X	X	X	X
Diary card [m]	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.				
Dosing					
Modakafusp alfa infusion [g]	X	X	X	X	X
Lenalidomide PO [h]	→[a]	→[a]	→[a]	→[a]	→[a]
Imaging Assessments *(local)*					
Bone imaging [l, n]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).				
Extramedullary disease imaging [l, o]	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).				
Clinical assessment of imaging response/status	Additional assessments to be done per the imaging schedule Section 9.9.				

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 2 Group 1 Arm 1 MM Maintenance Modakafusp Alfa IV and Lenalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**				
Cycle Day	C3D1	C4D1	C5D1	C6D1	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Safety Laboratory Assessments *(local analysis)*					
Chemistry [q]	X	X	X	X	X
Hematology [r]	X	X	X	X	X
Thyroid function [s]	X			X	X
Pregnancy test [v]	X	X	X	X	X
Disease Assessments					
Serum M-protein	X	X	X	X	X
24-hour urine M-protein [x]	(X)	(X)	(X)	(X)	(X)
Serum FLC assay	X	X	X	X	X
Immunofixation - serum and urine [y]	X	X	X	X	X
Quantification of Ig [z]	X	X	X	X	X
BMA/biopsy	Refer to Appendix B.				
Investigator assessment of disease response/status	X	X	X	X	X
Biologic Assessments *(central)*					
Serum sample for modakafusp alfa PK	Refer to Appendix C				
Serum sample for immunogenicity (ADA/NAb) [cc]	X	X	X	X	X

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 3 Group 2 Arm 2 RRMM Doublet Modakafusp Alfa IV and Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [b] and subject identification card issued	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
Height and weight [c]	X					X			
ECOG performance status	X					X			
12-lead ECG [d]	X	X		X		X		X	
Physical examination [e]	X	X		X		X		X	
Vital signs [f]	X	X		X		X		X	
Diary card [m]		X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.								

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 3 Group 2 Arm 2 RRMM Doublet Modakafusp Alfa IV and Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Dosing									
Modakafusp alfa infusion [g]		X				X			
Pomalidomide PO [i]		→[a]	→[a]	→[a]		→[a]	→[a]	→[a]	
Imaging Assessments *(local)*									
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).							
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).							
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule Section 9.9.							
Safety Laboratory Assessments *(local analysis)*									
Chemistry [q]	X	(X)	X	X	X	X	X	X	X
Hematology [r]	X	(X)	X	X	X	X	X	X	X
Thyroid function [s]	X								
Viral serologies [t]	X								
Urinalysis [u]	X								
Pregnancy test [v]	X	X	X	X	X	X			
ABO blood group and Rh factor, direct and indirect Coombs tests	X								

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 3 Group 2 Arm 2 RRMM Doublet Modakafusp Alfa IV and Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Disease Assessments									
Serum M-protein [w]	X	(X)		X		X		X	
24-hour urine M-protein [w, x]	X	(X)		(X)		(X)		(X)	
Serum FLC assay [w]	X	(X)		X		X		X	
Immunofixation - serum and urine [w, y]	(X)	(X)		X		X		X	
Quantification of Ig [w, z]	X	(X)				X			
Serum β_2 microglobulin	X								
BMA/biopsy	X	Refer to Appendix B.							
Investigator assessment of disease response/status						X			
Biologic Assessments *(central)*									
Serum sample for modakafusp alfa PK		Refer to Refer to Appendix C.							
Blood sample for flow cytometry [g, aa]		X [bb]	X	X	X	X [bb]	X	X	X
Serum sample for circulating biomarkers [g]		X [ii]	X	X	X				
Serum sample for immunogenicity (ADA/NAb) [cc]		X		X		X		X	
[redacted]									
Blood sample for RNA [g]		X [ii]	X	X	X				

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 4 Group 2 Arm 2 RRMM Doublet Modakafusp Alfa IV and Pomalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**				
Cycle Day	C3D1	C4D1	C5D1	C6D1	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Weight [c]	X	X	X	X	X
ECOG performance status	X	X	X	X	X
12-lead ECG [d]		X		X	X
Physical examination [e]	X	X	X	X	X
Vital signs [f]	X	X	X	X	X
Diary card [m]	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.				
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.				
Dosing					
Modakafusp alfa infusion [g]	X	X	X	X	X
Pomalidomide PO [i]	→[a]	→[a]	→[a]	→[a]	→[a]
Imaging Assessments *(local)*					
Bone imaging [l, n]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).				
Extramedullary disease imaging [l, o]	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).				
Clinical assessment of imaging response/status	Additional assessments to be done per the imaging schedule Section 9.9.				

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 4 Group 2 Arm 2 RRMM Doublet Modakafusp Alfa IV and Pomalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**				
Cycle Day	C3D1	C4D1	C5D1	C6D1	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Safety Laboratory Assessments *(local analysis)*					
Chemistry [q]	X	X	X	X	X
Hematology [r]	X	X	X	X	X
Thyroid function [s]	X			X	X
Pregnancy test [v]	X	X	X	X	X
Disease Assessments					
Serum M-protein	X	X	X	X	X
24-hour urine M-protein [x]	(X)	(X)	(X)	(X)	(X)
Serum FLC assay	X	X	X	X	X
Immunofixation - serum and urine [y]	X	X	X	X	X
Quantification of Ig [z]	X	X	X	X	X
BMA/biopsy	Refer to Appendix B.				
Investigator assessment of disease response/status	X	X	X	X	X
Biologic Assessments *(central)*					
Serum sample for modakafusp alfa PK	Refer to Appendix C.				
Serum sample for immunogenicity (ADA/NAb) [cc]	X	X	X	X	X

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 5 Group 2 Arm 3 RRMM Doublet Modakafusp Alfa IV and Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**		**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D11	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [b] and subject identification card issued	X									
Eligibility criteria	X									
Demographics	X									
Medical history	X									
Prior medication and treatment history	X									
Height and weight [c]	X						X			
ECOG performance status	X						X			
12-lead ECG [d]	X	X	X		X	X	X	X	X	X
Physical examination [e]	X	X	X		X	X	X	X	X	X
Vital signs [f]	X	X	X		X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.									
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.									

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 5 Group 2 Arm 3 RRMM Doublet Modakafusp Alfa IV and Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**		**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D11	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Dosing										
Modakafusp alfa infusion [g]		X					X			
Bortezomib SC [j]			X		X	X		X	X	X
Imaging Assessments *(local)*										
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).								
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).								
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule (Section 9.9).								
Safety Laboratory Assessments *(local analysis)*										
Chemistry [q]	X	(X)	X	X [dd]	X	X	X	X	X	X
Hematology [r]	X	(X)	X	X [dd]	X	X	X	X	X	X
Thyroid function [s]	X									
Viral serologies [t]	X									
Urinalysis [u]	X									
Pregnancy test [v]	X	X					X			
ABO blood group and Rh factor, direct and indirect Coombs tests	X									

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 5 Group 2 Arm 3 RRMM Doublet Modakafusp Alfa IV and Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**		**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D11	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Disease Assessments										
Serum M-protein [w]	X	(X)			X		X		X	
24-hour urine M-protein [w, x]	X	(X)			(X)		(X)		(X)	
Serum FLC assay [w]	X	(X)			X		X		X	
Immunofixation - serum and urine [w, y]	(X)	(X)			X		X		X	
Quantification of Ig [w, z]	X	(X)					X			
Serum β_2 microglobulin	X									
BMA/biopsy	X	Refer to Appendix B.								
Investigator assessment of disease response/status							X			
Biologic Assessments *(central)*										
Serum sample for modakafusp alfa PK		Refer to Appendix C.								
Blood sample for flow cytometry [g, aa]		X [bb]	X		X	X	X [bb]	X	X	X
Serum sample for circulating biomarkers [g]		X [ii]	X [bb]		X [bb]	X [bb]				
Serum sample for immunogenicity (ADA/NAb) [cc]		X			X		X		X	
[redacted]										
Blood sample for RNA [g]		X [ii]	X [bb]		X [bb]	X [bb]				

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Take For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 6 Group 2 Arm 3 RRMM Doublet Modakafusp Alfa IV and Bortezomib SC: Cycle 3 and Beyond

Study Period		**Treatment Phase**					
Cycle Day	C3-C8 D1	C3-C8 D8	C3-C8 D15	C3-C8 D22	C9 and Beyond D1	C9 and Beyond D8	C9 and Beyond D22
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Weight [c]	X				X		
ECOG performance status	X				X		
12-lead ECG [d]	X				X		
Physical examination [e]	X				X		
Vital signs [f]	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.						
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.						
Dosing							
Modakafusp alfa infusion [g]	X				X		
Bortezomib SC [j]		X	X	X		X	X
Imaging Assessments *(local)*							
Bone imaging [l, n]		Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).					
Extramedullary disease imaging [l, o]		Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).					
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule (Section 9.9).					

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 6 Group 2 Arm 3 RRMM Doublet Modakafusp Alfa IV and Bortezomib SC: Cycle 3 and Beyond

Study Period		**Treatment Phase**					
Cycle Day	C3-C8 D1	C3-C8 D8	C3-C8 D15	C3-C8 D22	C9 and Beyond D1	C9 and Beyond D8	C9 and Beyond D22
Safety Laboratory Assessments *(local analysis)*							
Chemistry [q]	X	X	X	X	X	X	X
Hematology [r]	X	X	X	X	X	X	X
Thyroid function [s]	X				X		
Pregnancy test [v]	X				X		
Disease Assessments							
Serum M-protein	X				X		
24-hour urine M-protein [x]	(X)				(X)		
Serum FLC assay	X				X		
Immunofixation - serum and urine [y]	X				X		
Quantification of Ig [z]	X				X		
BMA/biopsy	Refer to Section Appendix B.						
Investigator assessment of disease response/status	X				X		
Biologic Assessments *(central)*							
Serum sample for modakafusp alfa PK	Refer to Appendix C.						
Blood sample for flow cytometry (only at C3) [g, aa, bb]	X	X	X	X			
Serum sample for immunogenicity (ADA/NAb) [cc]	X				X		

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 7 Group 3 Arm A RRMM Triplet Modakafusp Alfa IV + Pomalidomide PO + Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [b] and subject identification card issued	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
Height and weight [c]	X					X			
ECOG performance status	X					X			
12-lead ECG [d]	X	X	X	X	X	X	X	X	X
Physical examination [e]	X	X	X	X	X	X	X	X	X
Vital signs [f]	X	X	X	X	X	X	X	X	X
Diary card [m]		X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.								

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 7 Group 3 Arm A RRMM Triplet Modakafusp Alfa IV + Pomalidomide PO + Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Dosing									
Modakafusp alfa infusion [g]		X				X			
Bortezomib SC [j]			X	X	X		X	X	X
Pomalidomide PO [i]		→	→	→		→	→	→	
Imaging Assessments *(local)*									
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).							
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).							
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule (Section 9.9.)							
Safety Laboratory Assessments *(local)*									
Chemistry [q]	X	(X)	X	X	X	X	X	X	X
Hematology [r]	X	(X)	X	X	X	X	X	X	X
Thyroid function [s]	X								
Viral serologies [t]	X								
Urinalysis [u]	X								
Pregnancy test [v]	X	X	X	X	X	X			
ABO blood group and Rh factor, direct and indirect Coombs tests	X								

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 7 Group 3 Arm A RRMM Triplet Modakafusp Alfa IV + Pomalidomide PO + Bortezomib SC: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Disease Assessments									
Serum M-protein [w]	X	(X)		X		X		X	
24-hour urine M-protein [w, x]	X	(X)		(X)		(X)		(X)	
Serum FLC assay [w]	X	(X)		X		X		X	
Immunofixation - serum and urine [w, y]	(X)	(X)		X		X		X	
Quantification of Ig [w, z]	X	(X)				X			
Serum β_2 microglobulin	X								
BMA/biopsy	X	Refer to Appendix B.							
Investigator assessment of disease response/status						X			
Biologic Assessments *(central)*									
Serum sample for modakafusp alfa PK		Refer to Refer to Appendix C.							
Blood sample for flow cytometry [g, aa]		X [bb]	X	X	X	X [bb]	X	X	X
Serum sample for circulating biomarkers [g]		X [ii]	X [bb]	X [bb]	X [bb]				
Serum sample for immunogenicity (ADA/NAb) [cc]		X		X		X		X	
[redacted]									
Blood sample for RNA [g]		X [ii]	X [bb]	X [bb]	X [bb]				

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 8 Group 3 Arm A RRMM Triplet Modakafusp Alfa IV+ Pomalidomide PO + Bortezomib SC: Cycle 3 and Beyond

Study Period	**Treatment Phase**						
Cycle Day	C3-C8 D1	C3-C8 D8	C3-C8 D15	C3-C8 D22	C9 and Beyond D1	C9 and Beyond D8	C9 and Beyond D22
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Weight [c]	X				X		
ECOG performance status	X				X		
12-lead ECG [d]	X				X		
Physical examination [e]	X				X		
Vital signs [f]	X	X	X	X	X	X	X
Diary card [m]	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.						
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.						
Dosing							
Modakafusp alfa infusion [g]	X				X		
Bortezomib SC [j]		X	X	X		X	X
Pomalidomide PO [i]	→	→	→		→	→	
Imaging Assessments *(local)*							
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).					
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).					
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule Sections 9.9.1 and 9.9.2.					

Property of Takeda. For noncommercial use only and subject to the applicable Terms of Use

Appendix A Table 8 Group 3 Arm A RRMM Triplet Modakafusp Alfa IV+ Pomalidomide PO + Bortezomib SC: Cycle 3 and Beyond

Study Period	**Treatment Phase**						
Cycle Day	C3-C8 D1	C3-C8 D8	C3-C8 D15	C3-C8 D22	C9 and Beyond D1	C9 and Beyond D8	C9 and Beyond D22
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Safety Laboratory Assessments *(local)*							
Chemistry [q]	X	X	X	X	X	X	X
Hematology [r]	X	X	X	X	X	X	X
Thyroid function [s]	X				X		
Pregnancy test [v]	X				X		
Disease Assessments							
Serum M-protein	X				X		
24-hour urine M-protein [x]	(X)				(X)		
Serum FLC assay	X				X		
Immunofixation - serum and urine [y]	X				X		
Quantification of Ig [z]	X				X		
BMA/biopsy	Refer to Appendix B.						
Investigator assessment of disease response/status	X				X		
Biologic Assessments *(central)*							
Serum sample for modakafusp alfa PK	Refer to Appendix C.						
Blood sample for flow cytometry (only at C3) [g, aa, bb]	X	X	X	X			
Serum sample for immunogenicity (ADA/NAb) [cc]	X				X		

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 9 Group 3 Arm D RRMM Triplet Modakafusp Alfa IV + Daratumumab SC + Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Informed consent [b] and subject identification card issued	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
Height and weight [c]	X					X			
ECOG performance status	X					X			
12-lead ECG [d]	X	X	X	X	X	X	X	X	X
Pulmonary function testing	X								
Physical examination [e]	X	X	X	X	X	X	X	X	X
Vital signs [f]	X	X	X	X	X	X	X	X	X
Diary card [m]		X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.								

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 9 Group 3 Arm D RRMM Triplet Modakafusp Alfa IV + Daratumumab SC + Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Dosing									
Modakafusp alfa infusion [g]		X				X			
Pomalidomide [i]		→	→	→		→	→	→	
Daratumumab SC [k]		X	X	X	X	X	X	X	X
Imaging Assessments *(local)*									
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).							
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).							
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule Section 9.9.							
Safety Laboratory Assessments *(local)*									
Chemistry [q]	X	(X)	X	X	X	X	X	X	X
Hematology [r]	X	(X)	X	X	X	X	X	X	X
Thyroid function [s]	X								
Viral serologies [t]	X								
Urinalysis [u]	X								
Pregnancy test [v]	X	X	X	X	X	X			
Blood group and Rh, direct and indirect Coombs tests	X								

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 9 Group 3 Arm D RRMM Triplet Modakafusp Alfa IV + Daratumumab SC + Pomalidomide PO: Screening, Cycle 1, and Cycle 2

Study Period	**Screening**	**Treatment Phase – Cycle 1**				**Treatment Phase – Cycle 2**			
Cycle Day		C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Disease Assessments									
Serum M-protein [w]	X	(X)		X		X		X	
24-hour urine M-protein [w, x]	X	(X)		(X)		(X)		(X)	
Serum FLC assay [w]	X	(X)		X		X		X	
Immunofixation - serum and urine [w, y]	(X)	(X)		X		X		X	
Quantification of Ig [w, z]	X	(X)				X			
Serum β_2 microglobulin	X								
BMA/biopsy	X	Refer to Appendix B.							
Investigator assessment of disease response/status						X			
Biologic Assessments *(central)*									
Serum sample for modakafusp alfa PK		Refer to Appendix C.							
Blood sample for flow cytometry [g, aa]		X [ii]	X [bb]	X [bb]	X [bb]	X [ii]	X [bb]	X [bb]	X [bb]
Serum sample for circulating biomarkers [g]		X [ii]	X [bb]	X [bb]	X [bb]				
Serum sample for immunogenicity (ADA/NAb) [cc]		X		X		X		X	
[redacted]									
Blood sample for RNA [g]		X [ii]	X [bb]	X [bb]	X [bb]				

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 10 Group 3 Arm D RRMM Triplet Modakafusp Alfa IV+ Daratumumab SC + Pomalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**								
Cycle Day	C3D1	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Weight [c]	X		X		X		X		X
ECOG performance status	X		X		X		X		X
12-lead ECG [d]			X				X		X
Physical examination [e]	X		X		X		X		X
Vital signs [f]	X	X	X	X	X	X	X	X	X
Diary card [m]	X	X	X	X	X	X	X	X	X
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF 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 last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first.								
	SAEs will be reported from signing of the ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy.								
Dosing									
Modakafusp alfa infusion [g]	X		X		X		X		X
Daratumumab SC [k]	X	X	X	X	X	X	X	X	X
Pomalidomide [i]	→	→	→	→	→	→	→	→	→
Imaging Assessments *(local)*									
Bone imaging [l, n]	(X)	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD) (Section 9.9.2).							
Extramedullary disease imaging [l, o]	(X)	Additional assessments for extramedullary disease per the imaging schedule (Section 9.9.1).							
Clinical assessment of imaging response/status		Additional assessments to be done per the imaging schedule Section 9.9.							

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 10 Group 3 Arm D RRMM Triplet Modakafusp Alfa IV+ Daratumumab SC + Pomalidomide PO: Cycle 3 and Beyond

Study Period	**Treatment Phase**								
Cycle Day	C3D1	C3D15	C4D1	C4D15	C5D1	C5D15	C6D1	C6D15	C7 and Beyond D1
Window Allowed	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**
Safety Laboratory Assessments *(local)*									
Chemistry [q]	X	X	X	X	X	X	X	X	X
Hematology [r]	X	X	X	X	X	X	X	X	X
Thyroid function [s]	X						X		X
Pregnancy test [v]	X		X		X		X		X
Disease Assessments									
Serum M-protein	X		X		X		X		X
24-hour urine M-protein [x]	(X)		(X)		(X)		(X)		(X)
Serum FLC assay	X		X		X		X		X
Immunofixation - serum and urine [y]	X		X		X		X		X
Quantification of Ig [z]	X		X		X		X		X
BMA/biopsy	Refer to Appendix B.								
Investigator assessment of disease response/status	X		X		X		X		X
Biologic Assessments *(central)*									
Serum sample for modakafusp alfa PK	Refer to Appendix C.								
Blood sample for flow cytometry [g, aa]	X [ii]	X [bb]							
Serum sample for immunogenicity (ADA/NAb) [cc]	X		X		X		X		X

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are after **Footnotes for SOE Appendix A Tables 1-11.**

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 11 All Groups: EOT and Follow-up

Study Period Visit Name	**EOT** [hh] 30 (+10) days after last dose or before the start of subsequent systemic anticancer therapy, whichever occurs first	**Follow-up (PFS)** [gg] Every 4±1 weeks	**Follow-up (OS)** [jj] Every 12±1 weeks
ECOG performance status	X		
12-lead ECG	X		
Physical examination [e]	X		
Vital signs	X		
Monitoring of concomitant medication and procedures	Recorded from signing of the ICF through 30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first		
AE reporting	Recorded from signing of the ICF through 30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first		
	SAEs will be reported from signing of the ICF through 30 (+10) days after last dose of study drug, even if the patient starts non protocol therapy	Only study drug-related SAEs will be reported	
Imaging Assessments *(local)*			
Bone imaging [l, n]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD)		
Extramedullary disease imaging [l, o, p]	Additional assessments for extramedullary disease per the imaging schedule		
Laboratory Assessments			
Chemistry [q]	X		
Hematology [r]	X		
Urinalysis [u]	X		
Pregnancy test [v]	X		
Thyroid function [s]	X		

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix A Table 11 All Groups: EOT and Follow-up

Study Period Visit Name	**EOT** [hh] 30 (+10) days after last dose or before the start of subsequent systemic anticancer therapy, whichever occurs first	**Follow-up (PFS)** [gg] Every 4±1 weeks	**Follow-up (OS)** [jj] Every 12±1 weeks
Disease Assessments			
Serum M-protein	(X) [ff]	X	X
24-hour urine M-protein [x]	(X) [ff]	(X)	(X)
Serum FLC assay	(X) [ff]	X	X
Immunofixation - serum and urine [y]	(X) [ff]	X	X
Investigator assessment of disease response/status	X	X	
Quantification of Ig [z]	(X) [ff]	X	X
BMA/biopsy	Refer to Appendix B.		
Blood sample for flow cytometry [aa]	X		
Serum sample for circulating biomarkers	X		
PK collection	Refer to Appendix C.		
Serum sample for immunogenicity (ADA/NAb) [cc]	X	X	
Survival			X
Subsequent therapy			X

Footnotes for all SOE tables (Treatment Arms 1, 2, 3, A, and D; EOT; and follow-up) are on after last page of SOE tables **Footnotes for SOE Appendix A Tables 1-11**.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Footnotes for SOE Appendix A Tables 1-11

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMA: bone marrow aspiration; BP: blood pressure; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D, d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCO_3-: bicarbonate; ICF: informed consent form; ID: identification; Ig: immunoglobulin; IRR: infusion-related reaction; IV: intravenous(ly); MM: multiple myeloma; MRI: magnetic resonance imaging; NAb: neutralizing antibody; OS: overall survival; PCR: polymerase chain reaction; PD: progressive disease; PET-CT: positron emission tomography–computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PO: oral(ly); QD: once daily; RBC: red blood cell; RRMM: relapsed/refractory multiple myeloma; SAE: serious adverse event; SC: subcutaneous(ly); SOE: schedule of events; T4: thyroxine; [redacted]; TSH: thyroid stimulating hormone; WBC: white blood cell.

Cross in parentheses "(X)" indicates test is to be performed only under certain circumstances as indicated in the associated footnote(s).

[a] Denotes continuously during each cycle. Lenalidomide will be taken PO QD continuously (D1-D28). Pomalidomide will be taken PO on Days 1-21.

[b] Written informed consent must be obtained before performing any protocol-specific procedure. Test results from routine clinical management are acceptable for screening if obtained within the specified time window.

[c] Height will be measured only at the screening visit.

[d] Standard local safety ECGs will be collected and read locally at screening, on dosing days during C1 and C2 (depending on the arms), and beyond every other cycle (ie, C4D1, C6D1, C8D1, etc).

[e] Physical examinations may be performed up to 1 day before treatment infusions. After screening, targeted physical examinations (symptom directed) may be performed.

[f] Vital signs are to be measured before starting the infusion and at completion of the infusion. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and BP. BP will be measured every 30 minutes (±5 minutes) during the first 4 infusions, at the end of all infusions, and at any moment the patient complains of symptoms consistent with an IRR.

[g] In case of an IRR, collect serum samples for circulating biomarkers, blood samples for flow cytometry, and blood samples for RNA.

[h] Lenalidomide dose will be 10 mg PO QD continuously (D1-D28) per Section 6.2.1.1. Participants with a uterus/ovary(ies) must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions, and for at least 4 weeks after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control beginning 4 weeks before initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 4 weeks after discontinuation of lenalidomide therapy. **Two negative pregnancy tests must be obtained before initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours before prescribing lenalidomide therapy; pregnancy tests should then be obtained weekly during the first month, and monthly thereafter in participants with regular menstrual cycles, or every 2 weeks in participants with irregular menstrual cycles.** Lenalidomide should be taken at about the same time each day. When both modakafusp alfa and lenalidomide are given on the same visit day, lenalidomide should not be administered at the same time as modakafusp alfa. (At least 30 minutes should elapse between the administration of the 2 drugs.)

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

[i] Pomalidomide dose will be 4 mg PO on Days 1-21 of each 28-day cycle per Section 6.2.2.1. Participants with a uterus/ovary(ies) must avoid pregnancy for at least 4 weeks before beginning pomalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks before initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide therapy. **Two negative pregnancy tests must be obtained before initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours before prescribing pomalidomide therapy; pregnancy tests should then be obtained weekly during the first month, and monthly thereafter in participants with regular menstrual cycles, or every 2 weeks in participants with irregular menstrual cycles.** Pomalidomide should be taken at about the same time each day. When both modakafusp alfa and pomalidomide are given on the same visit day, pomalidomide should not be administered at the same time as modakafusp alfa. (At least 30 minutes should elapse between the administration of the 2 drugs.)

[j] Bortezomib dose will be 1.3 mg/m^2 SC on Days 8, 15 and 22 of each 28-day cycle for the first 8 cycles and subsequently on Days 8 and 22 per Section 6.2.2.2.

[k] Daratumumab dose will be 1800 mg SC on Days 1, 8, 15, and 22 of Cycles 1 and 2; on Days 1 and 15 of Cycles 3 to 6; and then on Day 1 thereafter, per Section 6.2.3.2.

[l] The same assessment modality should be used throughout the study. Adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug can be used as the screening evaluation and do not need to be repeated.

[m] Patients receiving PO combination agents (lenalidomide or pomalidomide) will record doses taken in a diary provided by the site. The diary card will be given to patients on C1D1. The diary card will be reviewed by the study site per Section 9.7.12

[n] Imaging to assess bone disease is required for all patients at screening. If the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening. Low-dose whole-body CT is recommended over conventional skeletal survey for the evaluation of MM bone disease. Conventional skeletal survey can be used for the diagnosis of MM when whole-body CT or other novel imaging methods are not available. Additional assessments for bone disease can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD). The same modality for assessment should be used throughout the study.

[o] Imaging to assess extramedullary disease is required for all patients at screening by PET-CT, MRI, or CT scan. If the patient has adequate imaging test(s) performed within 5 weeks of the planned first dose of study drug, they can be used as baseline evaluations and do not need to be repeated as part of screening. If extramedullary disease is documented at screening, repeat imaging using the same modality every 12 weeks until a plateau or CR is reached, or as clinically indicated, and then at suspected progression. Imaging tests for patients with extramedullary disease should be performed if new symptoms suggest PD.

[p] For posttreatment follow-up of patients with extramedullary disease who stop treatment for reason other than PD, PET-CT scan, CT scan, or MRI scan should be performed every 12 weeks or if new symptoms suggest PD.

[q] Chemistry will consist of albumin, alkaline phosphatase, ALT, AST, bilirubin (total), blood urea nitrogen or urea, calcium, HCO_3- or CO_2, creatinine, chloride, glucose (nonfasting), lactate dehydrogenase, magnesium, phosphate, potassium, sodium, standard C-reactive protein, and urate. It is not necessary to repeat these tests on C1D1 predose if screening tests were done ≤4 days earlier.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

[r] Hematology will consist of hemoglobin, hematocrit, platelet count, leukocytes with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils) and ANC. See footnote [dd] for additional tests. It is not necessary to repeat these tests on C1D1 predose if screening tests were done ≤4 days earlier.

[s] Thyroid function tests will consist of TSH and free T4. These tests will be performed at screening, and **every 3 cycles thereafter** (ie, C3D1, C6D1, C9D1, etc) until EOT.

[t] Viral serologies will consist of hepatitis B serology (HBsAg, HBcAb, HBsAb) and will be performed at screening. For hepatitis B: patients with resolved infection (ie, patients who are HBsAg negative but positive for antibodies to anti-HBc and/or antibodies to anti-HBs) **must be screened** using real-time PCR measurement of HBV DNA levels. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

[u] Urinalysis (dipstick) will include bilirubin, glucose, ketones, leukocytes, nitrites, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic analysis only if clinically indicated: bacteria, RBCs, WBCs, casts, bacteria and crystals.

[v] Pregnancy testing (refer to Section 8.8.1).

- Screening: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug. A negative urine or serum pregnancy test will be required at screening (within 10 to 14 days before the start of study drug). A negative urine or serum pregnancy test is required at baseline (within 24 hours before the start of study drug).
- On-treatment: Participants of childbearing potential must have a negative urine or serum pregnancy test result within 72 hours before dosing on Day 1 of each cycle. If menstrual period is delayed, absence of pregnancy in patients of childbearing potential must be confirmed by a negative urine or serum pregnancy test.
- A urine or serum pregnancy test is required at EOT in participants of childbearing potential.
- Participants of childbearing potential in treatment arms with lenalidomide or pomalidomide must have negative pregnancy tests as defined in the prescribing information (2 negative tests must be obtained before initiating therapy). The first test should be performed within 10-14 days and the second test within 24 hours before therapy; pregnancy tests should then be obtained weekly during the first month, and monthly thereafter in participants with regular menstrual cycles, or every 2 weeks in participants with irregular menstrual cycles.

[w] Repeat at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

[x] Urine M-protein 24-hour urine sample required while on treatment and during follow-up only if urine M-protein is measurable at baseline (urine M-protein ≥200 mg/24 hours).

[y] Immunofixation of serum and/or urine may be omitted at screening if a previous local laboratory report for the serum and/or urine protein electrophoresis states that the observed monoclonal spike is consistent with one previously characterized by immunofixation and specifies the heavy chain and light chain previously identified. Immunofixation in serum and urine is required for patients evaluated for CR.

[z] A blood sample for quantification of Ig (IgM, IgG, and IgA) will be obtained. For the rare patient with known IgD or IgE MM, the quantitative test for that antibody should occur at the same time points throughout the treatment period and PFS follow-up period as quantitative Igs (in addition to quantitative IgM, IgG, and IgA).

[aa] Blood sample to be collected for centralized flow cytometry, [redacted].

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

[bb] Samples are to be collected predose (before administration of parenteral agents).

[cc] Blood samples for immunogenicity (ADA/NAb) testing will be collected before the dose on indicated visits while the patient remains in treatment, and at the EOT visit and follow-up visits for up to 1 year after EOT. In case of an IRR, blood draws should be performed for central evaluation of immunogenicity (see Section 9.10.5).

[dd] Ferritin and blood smear. Arm 3: At screening and C1D11, ferritin will be obtained in addition to the chemistry and hematology laboratory tests defined in footnotes q and r, respectively. At C1D11, schistocytes will be obtained in addition to the chemistry and hematology laboratory tests defined in footnotes q and r, respectively.

[redacted]

[ff] Repeat tests in parentheses only for patients terminating treatment due to PD, if they were not performed before for PD determination at the last visit, and for patients discontinuing due to treatment completion or CR if not performed before for CR confirmation.

[gg] Patients who discontinue for reasons other than PD will continue PFS follow-up every 4 weeks from the EOT visit until the occurrence of PD, death, the start of subsequent systemic antineoplastic therapy, study termination, or until 6 months after the discontinuation of study treatment, whichever occurs first.

[hh] EOT laboratory assessments are to be performed before the patient starts a new treatment or a maximum of 30 days (±10 days) after the last dose.

[ii] Samples to be collected predose (prior to administration of parenteral agents) and at 4 hours (±30 minutes) after the end of infusion of modakafusp alfa.

[jj] OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.2 Appendix B Bone Marrow Collection and Assessment Schedules

Appendix B Table 1 Bone Marrow Collection and Assessment Schedule for Group 1: MM Maintenance Modakafusp Alfa and Lenalidomide

Study Period	**Screening**	**Treatment Phase**	**Follow-up**	
Cycle Day			EOT	PFS Follow-up
Window Allowed	**≤21 d**	**±2 d**	**30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first**	**Every 4 weeks ±1 week**
BMA/biopsy for disease assessment (*local analysis*) [a, b]	X	Sample to be collected at susCR to confirm response, optional at the time of progression, and EOT.		
BMA for MRD (*central analysis*)	X	Sample to be collected 6 months, 1 year, and 2 years from start of study treatment.		
Fresh BMA sample (*central analysis*) [a]			(X)	

Footnotes follow Appendix B Table 2.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix B Table 2 Bone Marrow Collection and Assessment Schedule for Group 2: RRMM Doublet Combinations

Study Period	Screening	Treatment Phase	Follow-up	
Cycle Day		Suspected CR	EOT	PFS Follow-up
Window Allowed	**≤21 d**		**30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first**	**Every 4 weeks ±1 week**
BMA/biopsy for disease assessment (*local analysis*) [a, b]	X	Sample to be collected at susCR to confirm response, optional at the time of progression and EOT.		
BMA/biopsy for cytogenetics (*local analysis*) [a]	X			
BMA for MRD (*central analysis*) [c]		Sample to be collected at susCR and 6 months, 1 year, and 2 years following CR confirmation. Yearly sample collection if the patient had an MRD[-] result.		
Fresh BMA sample (*central analysis*) [b]	X		(X)	

Footnotes follow Appendix B Table 3.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix B Table 3 Bone Marrow Collection and Assessment Schedule for Group 3: RRMM Triplet Combinations

Study Period	Screening	Treatment Phase	Follow-up	
Cycle Day		Suspected CR	EOT	PFS Follow-up
Window Allowed	**≤21 days**		**30 (+10) days after last dose of study drug or the start of subsequent systemic anticancer therapy, whichever occurs first**	**Every 4 weeks ±1 week**
BMA/biopsy for disease assessment (*local analysis*) [a, b]	X	Sample to be collected at susCR to confirm response, optional at the time of progression and EOT.		(X)
BMA/biopsy for cytogenetics (*local analysis*) [a]	X			
BMA for MRD (*central analysis*) [c]	X	Sample to be collected at susCR and at 6 months, 1 year, and 2 years following CR confirmation. Yearly sample collection if the patient had an MRD[-] result.		
Fresh BMA sample (*central analysis*) [a]	X		(X)	

BMA: bone marrow aspirate, bone marrow aspiration; CR: complete response; EOT: end of treatment; MRD: measurable/minimal residual disease; MRD[-]: measurable/minimal residual disease negative; PFS: progression-free survival; susCR: suspected complete response.

For local analysis of disease assessment and cytogenetics at screening, a standard BMA biopsy drawn before consent is acceptable provided that the sample is collected within 5 weeks of the first dose.

[a] A BMA (1st or 2nd pull preferred) will be obtained at screening and optionally at relapse (for patients who have responded to treatment) [redacted]

[b] Optional BMA to be collected at EOT visit for central analysis for patients who have responded to therapy and progressed.

[c] If a patient has an MRD[-] result for any of the on-treatment assessments, this will trigger yearly evaluations of MRD until the patient progresses. However, if a patient does not have an MRD[-] result for any of the planned on-treatment assessments, no additional BMA for MRD will be required.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

17.3 Appendix C PK Sampling

Time Point	Modakafusp Alfa PK (Cycle 1 and Cycle 2)			
	Day 1 [a]	Day 8	Day 15	Day 22
Predose (within 30 min before administration of any SC or IV combination agent)	X			
End of infusion (±10 min)	X			
2 to 4 hours after end of infusion (±30 min)	X			
During the clinic visit		X [b]	X [b]	X [b]

IV: intravenous(ly); PK: pharmacokinetic(s); SC: subcutaneous(ly).

a. Modakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.

b. Blood samples for Day 8, 15, and 22 modakafusp alfa PK measurement will be collected during the clinic visit within 30 minutes before administration of any subcutaneous or IV combination agent.

Time Point	Modakafusp PK (Cycle 3 and Beyond) [a]	
	Day 1 [b]	EOT
End of infusion	X	
2 to 4 hours after end of infusion (±30 min)	X	
During the clinic visit		X

PK: pharmacokinetic(s); EOT: end of treatment.

a. Modakafusp alfa infusion. The timing of the morning visits should occur at approximately the same time as the morning infusion times on previous infusion visits.

b. Starting with Cycle 12, PK sampling will be performed every 3 cycles (C12D1, C15D1, C18D1, etc) until EOT.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.4 Appendix D Responsibilities of the Investigator

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

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

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

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

contact and receive written approval from the sponsor before disposing of any such documents.

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

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.5 Appendix E Elements of Informed Consent

In seeking informed consent, the following information shall be provided to each participant:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of participants involved in the study.
7. A description of the participant's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the participant may receive.
11. A description of any reasonably foreseeable risks or discomforts to the participant and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the participant or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the participant will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the participant or the participant's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the participant for participating in the study.
17. The anticipated expenses, if any, to the participant for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), participant's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the participant.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant otherwise is entitled, and that the participant or the

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

20. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
21. A statement that the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.
22. A statement that results of pharmacogenomics analysis will not be disclosed unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under participation in the study may be terminated.
24. A written participant authorization (either contained within the ICF or provided as a separate document) describing to the participant the contemplated and permissible uses and disclosures of the participant's personal information (including personal health information) for purposes of conducting the study. The authorization must contain the following statements regarding the uses and disclosures of the participant's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that participants agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the participant's identity will remain confidential in the event that study results are published.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

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

Patients with a uterus and ovary(ies) must meet 1 of the following:

- Postmenopausal for at least 2 years 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 (see Table 8.g) at the same time, from the time of signing of the ICF through 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Patients with a uterus and ovary(ies) must adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.
- Agree not to donate an egg or eggs (ova) or breastfeed a baby during the study through 7 days after the last dose of modakafusp alfa or through the period defined by the combination agent's label, whichever is longer.

Patients with testis(es), even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception (see Table 8.g) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, 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, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Patients with testis(es), even if surgically sterilized (ie, status postvasectomy), must:

- Agree not to donate sperm during the study and for 7 days after the last dose of modakafusp alfa, or through the period defined by the combination agent's label, whichever is longer.
- Also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

17.6 Appendix F Investigator Consent to the 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 UK, US, and Japan), including the following:

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

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.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

17.7 Appendix G IMWG Definition of MM and Response Criteria

IMWG criteria will be used for evaluating patient eligibility and response. Based on IMWG diagnostic criteria, MM is defined by the following (both criteria must be met):

1. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* **and**
2. 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 >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL.
     - 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 FLC ratio§ ≥100.
     - >1 focal lesion on MRI studies (at least 5 mm in size).

CT: computed tomography; FLC: free light chain; IMWG: International Myeloma Working Group; MM: multiple myeloma; MRI: magnetic resonance imaging; PET-CT: [^{18}F]fluorodeoxyglucose positron emission tomography with computed tomography.

* 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.

† 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 more in size (Rajkumar 2014).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Response Category	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; 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 [a].
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.
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.
PD	See text below.

BM: bone marrow; CR: complete response; FLC: free light chain; IMWG: International Myeloma Working Group; MR: minimal response; ORR: objective response rate; PD: progression of disease; 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. For this study, 2 consecutive BM assessments are not required.

[b] For relapsed/refractory myeloma only.

[c] These categories do not contribute to the ORR.

(Kumar et al. 2016)

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

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 do not need to be confirmed.

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

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

- Definite development of new bone lesions or soft tissue plasmacytomas OR ≥50% increase from nadir in sum of product of diameters of >1 soft tissue plasmacytoma OR ≥50% increase in the longest diameter of a previous soft tissue plasmacytoma >1 cm in its short axis or an unequivocal increase in the size of existing bone lesions.
- 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.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.8 Appendix H 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).

ECOG: Eastern Cooperative Oncology Group.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.9 Appendix I BOIN Design for Dose Escalation/De-escalation

The BOIN design will be implemented for dose escalation/de-escalation. The target toxicity rate for MTD is set to be $\phi = 0.25$ for MM maintenance and RRMM doublets and $\phi = 0.33$ for RRMM triplets, unless otherwise specified. Approximately 120 total patients will be enrolled to evaluate the dose escalation for a total of 6 arms (Zhou et al. 2021).

The operating characteristics of the BOIN design are evaluated with 1000 simulations (assuming various distributions of toxicity across dose levels) and presented in the following tables.

Group 1: MM - Maintenance Therapy

Appendix I Table 1 Simulation Settings for Arm 1: Modakafusp Alfa With Lenalidomide

	Dose 1	Dose 2	Dose 3	Dose 4	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1										
True DLT rate	0.25	0.42	0.50	0.59						
Selection %	69.8	22.4	3.2	0.2	13.4	69.8	25.8	44.7	55.3	4.4
% pts treated	44.7	44.9	9.2	1.2						
Scenario 2										
True DLT rate	0.10	0.25	0.40	0.62						
Selection %	21.1	55.7	21.0	1.9	16.3	55.7	22.9	47.5	27.1	0.3
% pts treated	25.4	47.5	23.0	4.1						
Scenario 3										
True DLT rate	0.02	0.10	0.25	0.42						
Selection %	0.10	24.9	56.8	18.2	17.1	56.8	18.2	39.8	14.3	0
% pts treated	7.3	38.6	39.8	14.3						
Scenario 4										
True DLT rate	0.05	0.08	0.12	0.25						
Selection %	1.0	8.2	32.1	58.7	16.3	58.7	0	26.4	0	0
% pts treated	5.8	30.9	36.9	26.4						

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

Group 2: RRMM - Doublet Combinations

Arms 2-4 in the doublet combinations for RRMM will have the same simulation settings as Arm 1 and therefore the same operating characteristics.

Group 3: RRMM - Triplet Combinations

Simulation settings for Arms A and D in the triplet combinations for RRMM are in Appendix I Table 2, Appendix I Table 3, Appendix I Table 4, and Appendix I Table 5.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Appendix I Table 2 Simulation Settings for Arms A and D in the Triplet Combinations for RRMM: Dose 1 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Dose 4	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1										
True DLT rate	0.33	0.50	0.58	0.67						
Selection %	68.0	16.5	2.2	0.1	12.1	68.0	18.8	67.6	32.4	13.2
% pts treated	67.6	28.1	4.1	0.2						
Scenario 2										
True DLT rate	0.14	0.33	0.50	0.70						
Selection %	26.2	52.7	19.9	0.7	16.2	52.7	20.6	43.1	17.7	0.5
% pts treated	39.2	43.1	16.2	1.5						
Scenario 3										
True DLT rate	0.02	0.15	0.33	0.50						
Selection %	0.8	25.0	56.9	17.3	17.5	56.9	17.3	33.3	11.3	0
% pts treated	20.6	34.8	33.3	11.3						
Scenario 4										
True DLT rate	0.05	0.11	0.18	0.33						
Selection %	1.0	7.3	38.3	53.4	17.7	53.4	0	24.4	0	0
% pts treated	20.9	25.8	28.8	24.4						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients;
RRMM: relapsed/refractory multiple myeloma.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix I Table 3 Simulation Settings for Arms A and D in the Triplet Combinations for RRMM: Dose 2 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Dose 4	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1										
True DLT rate	0.33	0.50	0.58	0.67						
Selection %	61.2	27.8	2.6	0	14.3	61.2	30.4	44.3	55.6	8.4
% pts treated	44.3	46.6	8.5	0.5						
Scenario 2										
True DLT rate	0.14	0.33	0.50	0.70						
Selection %	21.9	59.3	17.3	1.3	15.4	59.3	18.6	53.9	25.8	0.2
% pts treated	20.3	53.9	22.7	3.1						
Scenario 3										
True DLT rate	0.02	0.15	0.33	0.50						
Selection %	0.7	26.5	53.8	19.0	16.4	53.8	19.0	42.4	16.3	0
% pts treated	2.3	38.9	42.4	16.3						
Scenario 4										
True DLT rate	0.05	0.11	0.18	0.33						
Selection %	0.2	7.0	29.4	63.4	16.6	63.4	0	35.6	0	0
% pts treated	1.3	28.0	35.0	35.6						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients;
RRMM: relapsed/refractory multiple myeloma.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix I Table 4 Simulation Settings for Arms A and D in the Triplet Combinations for RRMM: Dose 3 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Dose 4	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1										
True DLT rate	0.33	0.50	0.58	0.67						
Selection %	51.7	28.2	11.8	0.3	16.2	51.7	40.3	30.8	69.2	8.0
% pts treated	30.8	33.5	32.1	3.6						
Scenario 2										
True DLT rate	0.14	0.33	0.50	0.70						
Selection %	15.5	55.4	28.1	0.8	15.7	55.4	28.9	39.0	48.9	0.2
% pts treated	12.1	39.0	42.8	6.1						
Scenario 3										
True DLT rate	0.02	0.15	0.33	0.50						
Selection %	0.4	21.1	60.6	17.9	15.3	60.6	17.9	55.2	24.1	0
% pts treated	1.1	19.5	55.2	24.1						
Scenario 4										
True DLT rate	0.05	0.11	0.18	0.33						
Selection %	0.1	2.7	32.0	65.2	14.6	65.2	0	49.4	0	0
% pts treated	0.2	4.8	45.6	49.4						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients;
RRMM: relapsed/refractory multiple myeloma.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Appendix I Table 5 Simulation Settings for Arms A and D in the Triplet Combinations for RRMM: Dose 4 as the Starting Dose

	Dose 1	Dose 2	Dose 3	Dose 4	Average sample size	Correct selection %	Overdose %	% patients at MTD	% patients overdosed	% early stop
Scenario 1										
True DLT rate	0.33	0.50	0.58	0.67						
Selection %	46.0	31.9	12.7	3.4	17.1	46.0	48.0	19.6	80.3	6.0
% pts treated	19.6	27.2	28.6	24.5						
Scenario 2										
True DLT rate	0.14	0.33	0.50	0.70						
Selection %	15.3	52.0	29.7	2.6	16.8	52.0	32.3	31.0	61.0	0.4
% pts treated	8.0	31.0	36.2	24.8						
Scenario 3										
True DLT rate	0.02	0.15	0.33	0.50						
Selection %	0.2	16.9	53.7	29.2	15.0	53.7	29.2	41.3	44.7	0
% pts treated	0.6	13.4	41.3	44.7						
Scenario 4										
True DLT rate	0.05	0.11	0.18	0.33						
Selection %	0	1.3	22.9	75.8	12.2	75.8	0	71.1	0	0
% pts treated	0	2.2	26.6	71.1						

DLT: dose-limiting toxicity; MTD: maximum tolerated dose; pts: patients;
RRMM: relapsed/refractory multiple myeloma.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

17.10 Appendix J Protocol History

Date	Amendment Number	Amendment Type	Region
03 April 2024	Amendment 4 v2	Substantial	Global
28 February 2024	Amendment 4 v1 (not implemented)	Substantial	Global
13 June 2023	Amendment 3	Substantial	Global
17 August 2022	Amendment 2	Substantial	Global
27 May 2022	Amendment 1	Substantial	Global
13 May 2022	Initial protocol EU v1	Nonsubstantial; Regional	European Union
01 April 2022	Initial protocol	Not applicable	Global

Protocol Amendment 1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

- Revise and/or clarify several procedures in the Schedules of Events (SOEs).
- Add an exclusion criterion for patients who have previously received modakafusp alfa.

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

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Cover page	EudraCT number added.	Number was not present.
2.	Section 5.1.3 [redacted] Table 9.a Primary Specimen Collections Section 13.1.5 Immunogenicity Analyses Appendix A Table 9 Appendix A Table 10	[redacted]	Assay not available.
3.	Section 6.2.3.2 Arm B MKP in RRMM Section 6.2.3.3 Arm C MDK in RRMM	Text regarding carfilzomib 20/56 intravenous (IV) mg/m^2 once weekly dosing schedule revised to include a full description of the carfilzomib dosing schedule in Group 3 (Arms B and C) within each modakafusp alfa IV dose level.	Revised for clarity and consistency.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	An exclusion criterion was added for previous modakafusp alfa treatment.	Update.
5.	Section 8.1.1.2 Postinfusion Medication Section 9.6.5 Vital Signs	Harmonized monitoring period procedures during infusions and postdose.	Update.
6.	Section 8.2.1 Definition of DLT-Evaluable Patients Section 13.1.1.3 DLT-Evaluable Analysis Set	Definition changed from "The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or have completed Cycle 1 dose of modakafusp alfa and at least 75% of the planned dose of the combination partners." to "The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or patients who received a full dose of modakafusp alfa and any amount of the planned dose of the combination partners and completed evaluation for DLT in Cycle 1."	Update to include patient with any dose of combination partners in the DLT-evaluable patient set.
7.	Section 9.6.12 Pulmonary Function Testing	Section added to describe the pulmonary function testing procedure to be used.	Correction.
8.	Section 9.6.13 Echocardiogram	Section added to describe the echocardiogram procedure to be used.	Correction.
9.	Section 9.8.2 Bone Imaging	Text regarding bone imaging updated.	Correction.
10.	Appendix A Schedules of Events Tables 1 to 19	Changed the term "Skeletal survey" to "Bone imaging" in all Schedule of Event (SOE) tables. Changed the term "CT, PET-CT, or MRI scan" to "Extramedullary imaging" in all SOE tables.	Editorial update.
11.	Appendix A Schedules of Events	Removed "if possible" from footnote *ee*.	Clarification.
12.	Appendix A Schedules of Events	Removed redundant footnote *nn*.	Correction.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	Appendix A Table 3	• Pomalidomide dispensation removed at Cycle (C)1 Day (D)22. • Serum free light chain (FLC) assay added at screening, C1D1, C1D15, and C2D15. • Immunofixation serum - urine added at C1D15, and C2D15. • Quantification of immunoglobulin (Ig) added at screening. • Quantification of Ig removed at C1D8, C1D15, C1D22, C2D8, C2D15, and C2D22. • Flow cytometry added at C2D1, C2D8, C2D15, and C2D22. • Investigator assessment of disease response removed at screening.	Corrections.
14.	Appendix A Table 5	Removed pregnancy test at C2D1.	Correction.
15.	Appendix A Table 9	Added pregnancy test at C1D1. Removed thyroid function at C1D1 and C2D1.	Correction.
16.	Appendix A Table 11	Removed pregnancy test at C2D8, C2D15, and C2D22.	Correction.
17.	Appendix A Schedules of Events Tables 11 to 19	"Serum sample for immunogenicity (ADA)" changed to "Serum sample for immunogenicity (ADA/NAb)."	Editorial update for consistency.
18.	Appendix A Schedules of Events Tables 1 to 19	Added row titles "Disease Assessments" and "Biologic Assessments" in all SOE tables.	Editorial update.
19.	Appendix A Schedules of Events Tables 1 to 19	Added row for serum β_2 microglobulin at screening.	Editorial update.
20.	Appendix A Schedules of Events Tables 1 to 19	[redacted]	Correction.
21.	Appendix A Schedules of Events Tables 1 to 19	Timing of screening assessments clarified in footnote *a.*	Clarification.
22.	Appendix C Table 2 PK Sampling: Cycles 3 and Beyond	Pharmacokinetics (PK) at end of treatment (EOT), which is already in Appendix A Table 19, added in Appendix C Table 2.	Editorial update for consistency.

Property of Takeda For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 2 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Remove modakafusp alfa and daratumumab arm (Arm 5 in Group 2 relapsed and refractory multiple myeloma [RRMM] Doublets).
- Remove secondary objectives relating to daratumumab pharmacokinetics (PK).
- Reduce the modakafusp alfa starting dose.
- Revise the prior therapy inclusion criterion.
- Update pregnancy testing timepoints and modalities, and contraception language (period of contraception and method).
- Update imaging assessment schedules.
- Remove baseline human immunodeficiency (HIV) and hepatitis C virus (HCV) testing.

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

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	2.0 STUDY SUMMARY	Removed all references to daratumumab doublet arm. Removed secondary objective regarding daratumumab PK. Number of subjects and arms updated. Modakafusp alfa dose updated.	Food and Drug Administration (FDA) comment and harmonization with inclusion criteria in Study TAK-573-2001.
2.	3.4 Corporate Identification	Section added per new template	New template
3.	4.4.1.1 Rationale for Modakafusp Alfa Dose	Added rationale for starting dose at 80 mg.	Per FDA feedback on Study TAK-573-2001.
4.	4.2.4.3 TAK-573-2001	Added section on Study TAK-573-2001.	Update.
5.	4.5.1.2 Clinical Safety Summary	Updated safety information	Update.
6.	5.1.2 Secondary Objectives	Removed secondary objective regarding daratumumab PK for Group 2 RRMM Doublets.	Arm 5 was removed from protocol (Modakafusp alfa-Daratumumab arm). This arm will be included in another study (TAK-573-2001).

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7.	6.2 Overview of Combination Therapy Groups and Dose Regimens	Added tables for combination regimens.	Clarification.
8.	6.1 Overview of Study Design Appendix A Schedules of Events	Removed Arm 5: Modakafusp alfa + daratumumab (MD) in RRMM.	This arm will be included in another study (TAK-573-2001).
9.	6.1 Overview of Study Design 6.3.1 Group 1: NDMM Maintenance 6.3.2 Group 2: RRMM Doublets 6.3.3 Group 3: RRMM Triplets 6.4 Number of Patients 13.3 Determination of Sample Size Appendix I BOIN Design for Dose Escalation/De-escalation	Sample size increased.	New dose cohort was added.
10.	6.2 Overview of Combination Therapy Groups and Dose Regimens	Changed modakafusp alfa starting dose to 80 mg in all arms and added 1 dose level (modakafusp alfa 60 mg).	Per FDA feedback on study TAK-573-2001.
11.	6.4 Number of Patients	Clarified replacement of non-dose-limiting toxicity (DLT) evaluable patients.	Clarification.
12.	6.5.4 Definition of End of Study/Study Completion and Planned Reporting	Details added regarding termination of the study.	Update.
13.	7.1 Inclusion Criteria	Changed inclusion Criterion 3c to "For Group 2 RRMM doublet arms only: Patients who have received at least 3 prior lines of antimyeloma therapy including at least 1 PI, 1 IMiD and 1 anti-CD38 mAb drug, or who are triple refractory to a PI, an IMiD and an anti-CD38 mAb drug regardless of the number of prior line(s) of therapy." Changed inclusion Criterion 3d to "For Group 3 RRMM triplet arms only: Patients who have received 1 to 3 prior lines of antimyeloma therapy including at least 1 PI and 1 IMiD, and who are not refractory to the combination partners."	FDA comment and harmonization with inclusion criteria in TAK-573-2001.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	7.1 Inclusion Criteria	Serum creatinine was removed from laboratory tests required at enrollment.	Update.
15.		Electronic consent was added.	Update.
16.	7.1 Inclusion Criteria	Criterion regarding nonsecretory multiple myeloma (MM) was removed.	Update.
17.	9.4 Informed (e)Consent	Criterion regarding usage of drugs that prolong the QT interval was removed.	Update.
18.		Criterion regarding current/prior use of immunosuppressive medications was removed.	Update.
19.	7.2 Exclusion Criteria	Two criteria regarding cardiovascular history were revised.	Update.
20.	8.1.1.3 Prophylaxis Against Risk of Infection	"…or as recommended with specific agents as described below.:" was added.	Update.
21.	8.3 Prohibited Medications and Procedures	Heading added to separate prohibited from permitted medications.	Clarification.
22.	8.4 List of European Union Auxiliary Medicinal Products Used in the Trial Other Than the Investigational Products	Section added per new template	New template.
23.	8.5.2 Intrapatient Dose Escalation	Text added regarding potential modakafusp alfa dose escalation.	Clarification.
24.	8.8.1 Contraception and Pregnancy Avoidance Procedures	Time frames and safety language were updated.	Update.
25.	9.7.15.1 Clinical Laboratory Tests	Details regarding transgender patients added.	Update.
26.	9.7.6 Pregnancy Test Appendix A Schedules of Events	Updated pregnancy testing by adding monthly pregnancy tests for all arms. Updated pregnancy testing to either serum or urine tests for all pregnancy testing.	Monthly pregnancy testing was required by health authorities on another TAK-573 study. Harmonization of the timepoints and methods through TAK-573 studies.
27.	9.7.15.1 Clinical Laboratory Tests Appendix A Schedules of Events	Remove HIV and HCV.	Harmonization with the TAK-573-2001 study.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
28.	9.9.1 Extramedullary Disease Imaging Appendix A Schedules of Events	Updated schedule of assessment from every 2 cycles to every 3 cycles if lesion at baseline.	Harmonization with standard-of-care (SOC) and other TAK-573 studies.
29.	9.9.2 Bone Imaging Appendix A Schedules of Events	Updated schedule of assessment from every 2 cycles to at the investigator's discretion.	Harmonization with SOC and other TAK-573 studies.
30.	Table 9.a Primary Specimen Collections 13.1.4 PK Analysis Appendix C PK Sampling	Remove daratumumab PK analysis for RRMM Doublets.	Arm 5 was removed from protocol (modakafusp alfa-daratumumab arm). This arm will be included in another study (TAK-573-2001).
31.	AE Definition	Definition revised to comply with new template.	Update.
32.	10.1.4 SAEs	Definition revised and text streamlined to comply with new template.	Update.
33.	10.2 Procedures for Reporting and Recording AEs and SAEs	Section revised and text streamlined to comply with new template. Fax numbers removed.	Update.
34.	Prior Section 10.2.8.5 Reporting of Abnormal Liver Function Tests	Section removed as no longer applicable.	Update.
35.	10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Section added	Update.
36.	14.2 Protocol Deviations	Clarification added regarding assessment of protocol deviations.	Update.
37.	Appendix A Schedules of Events	Removed urinalysis after CxD1 from all arms.	Harmonization with TAK-573-2001.
38.	Appendix A Schedules of Events	Removed thyroid function at C1D1 from Group 3 Arm A.	Correction.
39.	Previous Appendix I removed.	Examples of QT Interval Prolonging Agents.	Update.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

- Revise the study design.
- Update clinical data from ongoing modakafusp alfa studies.
- Close the combination arm with carfilzomib and add contraindications to concurrent carfilzomib and modakafusp alfa treatment.
- Add event-free survival (EFS) as a secondary endpoint.
- Revise the pomalidomide and bortezomib dosing schedules.
- Clarify instructions for the administration of combination agents.
- Clarify the collection of biomarker, pharmacodynamic, and immunogenicity samples.

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

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Cover page 2.0 STUDY SUMMARY	Added ClinicalTrials.gov identifier**.**	Regulatory update.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
2.	2.0 STUDY SUMMARY 5.3.2 Secondary Endpoints 5.3.3 [redacted] 6.0 STUDY DESIGN 7.1 Inclusion Criteria 13.0 STATISTICAL METHODS Appendix A Schedules of Events	Group 1 was modified. Eligibility changes: • Requirement for newly diagnosed multiple myeloma (MM) was removed. • Patients must not have started lenalidomide maintenance before enrollment. • Measurable disease at diagnosis no longer required. • Achievement of major clinical response no longer required. • Tandem transplant allowed. • Patients may start maintenance therapy as early as 60 days after transplantation and up to 180 days after transplantation or consolidation. NDMM (newly diagnosed multiple myeloma) maintenance was changed to MM maintenance throughout the protocol. Per investigator assessment was added to the secondary endpoint of overall response rate. [redacted]	Study design revision per investigator feedback.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
3.	2.0 STUDY SUMMARY 4.5.2 Benefit-Risk Profile of the Combination Agents 6.1 Overview of Study Design 6.2.2.3 Arm 4 MK in RRMM (Closed to Enrollment) 6.2.3 Group 3: RRMM Triplets 7.1 Inclusion Criteria 8.1.2.4 Daratumumab Administration, Premedications and Prophylaxis 13.3 Determination of Sample Size Appendix A Schedules of Events Appendix I BOIN Design for Dose Escalation/De-escalation	Carfilzomib was removed as a combination agent, and treatment arms that included carfilzomib were closed. • Arm 4 was closed to enrollment. • Arms B and C were removed from the protocol. • Content describing or related to carfilzomib and Arms 4, B, and C was removed. (Previous Sections 4.3.4, 4.4.2.4, and 9.7.13 were deleted.) • Study schema was revised.	Concurrent modakafusp alfa and carfilzomib treatment is contraindicated due to safety events.
4.	2.0 STUDY SUMMARY 5.1 Objectives 5.3 Endpoints 13.1.3.2 Group 2 and Group 3: RRMM Doublets and Triplets	Secondary [redacted] objectives and endpoints for Groups 2 and 3 were combined. The clinical benefit rate endpoint was removed as a secondary endpoint for Groups 2 and 3. Event-free survival (EFS) was added as a secondary endpoint for Groups 2 and 3.	Clarification and revision of study design.
5.	2.0 STUDY SUMMARY 6.1 Overview of Study Design 6.3 Dose Escalation/De-escalation 6.4 Number of Patients 13.3 Determination of Sample Size Appendix I BOIN Design for Dose Escalation/De-escalation	Sample size was updated to align with changes in study arms. Total sample size is approximately 120 patients: approximately 18 patients in Arm 1, 66 patients in the RRMM doublet arms, and 36 patients in the RRMM triplet arms.	Harmonization with aforementioned study design changes.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
6.	2.0 STUDY SUMMARY 6.2.2 Group 2: RRMM Doublets 6.2.3 Group 3: RRMM Triplets 6.3.2 Group 2: RRMM Doublets	New doses for pomalidomide (2 and 3 mg) were added.	Exploration of other dosing in the arm with pomalidomide.
7.	4.2.1 Mechanism of Action	Text describing the mechanism of action of modakafusp alfa was modified.	Update.
8.	4.2.4.1 TAK-573-1501 4.2.4.2 TAK-573-1001 4.4.1.1 Rationale for Modakafusp Alfa Dose 4.5.1 Benefit-Risk Profile of Modakafusp Alfa 4.5.1.2 Clinical Safety Summary	Text was updated with more-recent clinical data from Study TAK-573-1501 and Study TAK-573-1001.	Clinical update.
9.	4.2.4 Clinical Experience 4.2.4.3 TAK-573-2001 4.4.1.1 Rationale for Modakafusp Alfa Dose	Updated status of Study TAK-573-2001.	Update.
10.	4.2.4.4 TAK-573-1502 Arm 4	Safety events with concurrent modakafusp alfa and carfilzomib treatment were described in a new section.	Concurrent modakafusp alfa and carfilzomib treatment is contraindicated due to safety events.
11.	4.4.1.1 Rationale for Modakafusp Alfa Dose	Guidelines for the use of modakafusp alfa with concurrent anticoagulation were added.	Safety update.
12.	4.4.2.2 Pomalidomide	Text detailing the starting dose for pomalidomide was added as well as a literature reference for the lower pomalidomide dose.	Update.
13.	4.5.2 Benefit-Risk Profile of the Combination Agents 7.1 Inclusion Criteria	Instructions and precautions for pomalidomide were expanded.	Clinical update.
14.	6.3.1 Group 1: MM Maintenance 6.3.2 Group 2: RRMM Doublets 6.3.3 Group 3: RRMM Triplets	Bayesian Optimal Interval decision tables to guide escalation and de-escalation decisions and descriptions were added.	Statistical update.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
15.	6.2.2.2 Arm 3 MV in RRMM 8.1.2.3 Bortezomib Administration, Premedications and Prophylaxis Appendix A Schedules of Events	Bortezomib dosing schedule was revised.	Harmonization with aforementioned study design changes and safety update.
16.	6.2.2.2 Arm 3 MV in RRMM	Staged enrollment was added for Arm 3.	Study design update.
17.	6.5.1 Duration of an Individual Patient's Study Participation	Patients in Group 2 and Group 3 may receive modakafusp alfa in combination with associated agents until disease progression, unacceptable toxicity, or until any other discontinuation criterion is met, whichever occurs first.	Clarification.
18.	7.1 Inclusion Criteria #9	Prohibited prior treatments and washout periods were revised as follows. The minimal interval between the last dose of any of the following treatments/procedures and the first dose of study treatment must be at least: Bispecific antibodies 28 days Any investigational anticancer therapy product 28 days Clarified other inclusion criteria.	Clinical update and clarification.
19.	7.1 Inclusion Criteria 6.2.2 Group 2: RRMM Doublets	The eligibility requirement for estimated creatinine clearance is ≥60 mL/min (Cockcroft-Gault formula) for the first 3 patients in Arm 3.	Safety update.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
20.	7.1 Inclusion Criteria 8.1.2.1 Lenalidomide Administration, Premedications and Prophylaxis 8.1.2.2 Pomalidomide Administration, Premedications and Prophylaxis 8.8 Precautions and Restrictions 9.7.6 Pregnancy Testing	Contraception guidelines were expanded to include mandatory adherence to any treatment-specific pregnancy prevention program	Regulatory and safety update.
21.	7.2 Exclusion Criteria	Clarified exclusion criteria. For the criterion related to history of treatment discontinuation related to treatment-related toxicity, added "For the lenalidomide arm: The patient is intolerant to lenalidomide."	Clarification.
22.	8.1 Study Drug Administration	Timing of administration of pomalidomide and lenalidomide added.	Clarification.
23.	8.1.1.1 Premedications Appendix A Schedules of Events	Time frames for premedication were removed, and the timing of premedications was clarified.	Update based on ongoing clinical experience with modakafusp alfa.
24.	8.1.2.1 Lenalidomide Administration, Premedications and Prophylaxis	Inserted "Lenalidomide may increase digoxin plasma levels."	Update.
25.	8.1.2.4 Daratumumab Administration, Premedications and Prophylaxis Appendix A Schedules of Events	Section 8.1.2.4, previously *Carfilzomib Administration, Premedications and Prophylaxis*, was deleted. Section 8.1.2.4 is now as shown. Text added: No dose reduction is permitted for daratumumab.	Clinical update.
26.	8.3 Prohibited Medications and Procedures	Live vaccines are prohibited 30 days before the first administration of study drug and for 90 days after the completion of study treatment.	Response to a European Union health authority.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
27.	8.3 Prohibited Medications and Procedures	Carfilzomib was added to the list of prohibited medications.	Concurrent modakafusp alfa and carfilzomib treatment is contraindicated due to safety events.
28.	8.5 DLTs	The evaluation period for dose-limiting toxicity (DLT) may be increased as needed for safety reasons.	Because of the safety events with carfilzomib, flexible language was added for the DLT evaluation period.
29.	8.5.1 Definition of DLT-Evaluable Patients 13.1.1.3 DLT-Evaluable Analysis Set	The DLT-evaluable analysis set will include patients who experienced a DLT in Cycle 1 in the treatment phase of the study or patients who received a full dose of modakafusp alfa and at least 75% of the planned dose of the combination partners and completed evaluation for DLT in Cycle 1.	Clarification.
30.	8.6.1 Modakafusp Alfa and Combination Agent(s)	Dose modification and laboratory value requirements for treatment cycle guidelines were expanded.	Clinical update.
31.	9.10.5 Immunogenicity Sample Collection	Text describing handling of infusion-related reactions was expanded.	Clinical update.
32.	9.7.3 Physical Examination Appendix A Schedules of Events	Physical examinations after the screening visit can be symptom directed. In Group 3 For Cycle 3 and beyond, weight assessment, Eastern Cooperative Oncology Group assessment, and physical examination were removed from all days except Day 1 of each cycle.	Per input from an investigator, a comprehensive physical examination is not necessary at each visit.
33.	9.7.5 Vital Signs Appendix A Schedules of Events	Timing of blood pressure measurements was clarified.	Clinical update.
34.	9.7.13.2 Subject Identification Card Appendix A Schedules of Events	Patient identification cards will be provided to all patients.	Information for healthcare providers in the event a patient requires a blood transfusion.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
35.	9.7.14 Clinical Laboratory Procedures and Assessments	Hepatitis testing was clarified.	Previous text was imprecise. Text related to hepatitis testing was in only the exclusion criteria. It was added in this section for clarification.
36.	9.7.14 Clinical Laboratory Procedures and Assessments Appendix A Schedules of Events	ABO blood group, Rh factor, and direct and indirect antiglobulin tests were added.	Modakafusp alfa has been shown to interfere with serological testing due to binding to CD38 on red blood cells, which results in positive direct and indirect antiglobulin tests.
37.	9.7.14 Clinical Laboratory Procedures and Assessments Appendix A Schedules of Events	Collection was changed to free thyroxine (T4) instead of T4 and T3 (triiodothyronine).	Clinical clarification.
38.	9.7.14 Clinical Laboratory Procedures and Assessments Appendix A Schedules of Events	Ferritin and schizocytes tests were added for Arm 3. Safety laboratory tests were added at Cycle 1 Day 1 and Cycle 1 Day 11.	Clinical safety update.
39.	9.9.1 Extramedullary Disease Imaging 9.9.2 Bone Imaging	Language was added to describe future imaging central collection/ analysis if needed.	Internal committee request.
40.	9.9.7.2.1 BMA for MRD Assessment Appendix A Schedules of Events	Condensed information about time points for bone marrow aspiration.	Clarification.
41.	9.10.1 Primary Specimen Collection for PK, Pharmacodynamic, and Biomarker Assessments 9.10.3 [redacted] Appendix A Schedules of Events	Collection of biomarker samples was clarified. [redacted]	[redacted]
42.	9.10.3 [redacted] 9.10.3.2 [redacted] Appendix A Schedules of Events	[redacted]	Administrative clarification.
43.	9.10.3.2 [redacted]	[redacted].	[redacted].

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
44.	9.10.1 Primary Specimen Collection for PK, Pharmacodynamic, and Biomarker Assessments 9.10.4 [redacted] Appendix A Schedules of Events	Collection of [redacted] immunogenicity samples was clarified.	[redacted] neutralizing antibody was added to immunogenicity collections.
45.	2.0 STUDY SUMMARY 13.1.1.6 MRD Analysis Set 13.1.3 Efficacy Analysis	Analysis set for minimal/measurable residual disease was clarified.	Statistical update.
46.	13.1.3.2 Group 2 and Group 3: RRMM Doublets and Triplets	Clinical benefit rate (CBR) was replaced by event-free survival (EFS), and EFS was defined.	Clarification of a new endpoint.
47.	Appendix A Schedules of Events Appendix B Bone Marrow Collection and Assessment Schedules Appendix C PK Sampling	Footnotes were streamlined, clarified, or updated.	Clarification and update.
48.	Appendix A Schedules of Events	Visit schedule was clarified. For the arm with daratumumab, visits for Cycle 3 and beyond are as follows: Cycle 3 through Cycle 6 on Days 1 and 15 and Cycle 7 and beyond on Day 1. For the arms with bortezomib, visits for Cycle 3 and beyond are as follows: Cycle 3 through Cycle 8 on Days 1, 8, 15, and 22 and Cycle 9 and beyond on Days 1, 8, and 22.	Aligned with the dosing schedule of bortezomib and daratumumab.
49.	Appendix C PK Sampling	The pharmacokinetics sampling schedule was updated to every 3 cycles starting with Cycle 12 instead of every cycle.	Study design update.
50.	Appendix G IMWG Definition of MM and Response Criteria	Definitions were updated.	Update.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 Summary and Rationale (Not Implemented)

This section describes the changes in reference to the protocol incorporating Amendment 4 v1 (not implemented). As of 20 November 2023, Takeda decided to discontinue the development of modakafusp alfa, including Study TAK-573-1502. These decisions were made due to strategic reasons and not due to any safety concerns with modakafusp alfa. Following the implementation of Amendment 4, the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients.

Upon implementation of this amendment, activities will be limited to dosing of study drug and any modifications to administration and data collection requirements will be limited to the following safety assessments: all serious adverse events (regardless of causality, including all deaths), any adverse event (AE) leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required. Given what is already known regarding the safety profile of modakafusp alfa based upon all previous data collection, further collection and reporting of Grade ≤2 AEs is not expected to result in a change to patient management. Treating physicians will monitor and manage patients according to standard of care, in order to ensure overall patient safety.

All central laboratory and investigator assessments of response and progression for protocol purposes are discontinued. Patients will not be followed for the progression-free survival (PFS) or overall survival (OS) follow-up periods, as PFS and OS will no longer be collected. Pharmacokinetic assessments will no longer be performed or recorded. Local laboratory assessments should be performed per local standard of care, and recording of AEs in the electronic case report form will be limited to AEs leading to dose modification or discontinuation of study drug. See the updated Schedule of Events—Amendment 4 and beyond (Appendix A Table 1) for more detailed information.

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

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	2.0 STUDY SUMMARY	The purpose and rationale for Protocol Amendment 4 was added.	Clarification

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
2.	2.0 STUDY SUMMARY 5.1.2 Secondary Objectives 5.1.3 [redacted] 5.3.2 Secondary Endpoints 5.3.3 [redacted]	"Following the implementation of Protocol Amendment 4 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 4 and Beyond (Appendix A Table 1)." was added to the Secondary [redacted] Objectives and Endpoints for use after the implementation of Protocol Amendment 4.	Updated objectives and endpoints to note that data collected for them would no longer be collected after implementation of Protocol Amendment 4.
3.	6.1 Overview of Study Design	The purpose and rationale for the implementation of Protocol Amendment 4 was added. "Prior to Implementation of Protocol Amendment 4:" was added before text characterizing the Overview of Study Design for use prior to implementation of Protocol Amendment 4.	Clarification.
4.	6.2 Overview of Combination Therapy Groups and Dose Regimens 6.3 Dose Escalation/De-escalation 6.4 Number of Patients 6.5 Duration of the Study	"Following the implementation of Protocol Amendment 4 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 4 and Beyond (Appendix A Table 1)." was added throughout the Study Design section.	Clarification.
5.	6.5.3 Posttrial Access	"After the data cutoff date, ongoing patients must transition to the Posttrial Access program once it becomes available in their country." Was added to the Posttrial Access section.	Clarification.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
6.	6.5.4 Definition of End of Study/Study Completion and Planned Reporting	"Following the implementation of Protocol Amendment 4 patients will not be followed for the PFS or OS follow-up periods, as PFS and OS will no longer be collected as outlined in Section 1.3." was added to the Definition of End of Study for use after the implementation of Protocol Amendment 4. Language about premature termination of the study was added to match other trials in the program.	Clarification.
7.	8.0 STUDY DRUG	Section "8.4 List of European Union Auxiliary Medicinal Products Used in the Trial Other Than the Investigational Products" was removed.	As per the latest EU CTR guidance from EMA, all EU-CTR specific protocol changes will be made in the substantial modification step after EU CTR transition (as needed).
8.	9.0 STUDY CONDUCT	A description of the data collection requirements was added that will be implemented in Protocol Amendment 4.	Clinical updates.
9.	9.7 Study Procedures	A description of the data collection requirements and changes to study procedures was added that will be implemented in Protocol Amendment 4.	Clinical updates.
10.	9.7.3 Physical Examination 9.7.5 Vital Signs 9.7.6 Pregnancy Testing 9.7.9 ECOG Performance Status 9.7.11 12-Lead ECG 9.7.14 Clinical Laboratory Procedures and Assessments 9.7.14.1 Clinical Laboratory Tests	"Following the implementation of Protocol Amendment 4 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 4 and Beyond (Appendix A Table 1)." was added to the relevant Study Procedure section for use after the implementation of Protocol Amendment 4.	Clinical updates.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
11.	9.7.7 Concomitant Medications and Procedures	"Upon implementation of Protocol Amendment 4, concomitant medications and procedures will not be recorded in the eCRF." was added for use after the implementation of Protocol Amendment 4.	Clinical updates.
12.	9.7.8 AE Monitoring	"Upon implementation of Protocol Amendment 4 (see Section 1.3), AE data collection will be limited to the following: all SAEs, any AE leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). Refer to the Updated SOE - Amendment 4 (Appendix A Table 1) for details." was added for use after the implementation of Protocol Amendment 4.	Clinical updates.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
13.	9.7.14 .Clinical Laboratory Procedures and Assessments 9.7.14.1 Clinical Laboratory Tests	"Following the implementation of Protocol Amendment 4 (see Section 1.3), data collection will be limited to the safety assessments outlined in the updated Schedule of Events—Protocol Amendment 4 and Beyond (Appendix A Table 1). Per Protocol Amendment 4, local laboratory evaluations should be entered into the eCRF only if required to document a TEAE. For dosing decisions, response assessment, and all other safety assessments for the patient, local hematology and clinical chemistry laboratory results should be used and do not need to be entered into the eCRF. Local laboratory evaluations may be performed according to local SOC (ie, for acute management of TEAEs), per the investigator's judgment of SOC." was added for use after the implementation of Protocol Amendment 4.	Clinical updates.
14.	9.9 Disease Assessment 9.9.1 Extramedullary Disease Imaging 9.9.2 Bone Imaging 9.9.3 Quantification of Igs 9.9.4 Quantification of M-Protein in Serum and Urine 9.9.5 Serum FLC Assay 9.9.6 Immunofixation of Serum and Urine 9.9.7 BMA 9.9.7.1.1 Disease Assessment 9.9.7.1.2 Cytogenetics 9.9.7.2 Central Laboratory Evaluations	"Following the implementation of Protocol Amendment 4 (see Section 1.3), all laboratory and investigator assessments of response and progression for protocol purposes are discontinued. Patients should otherwise be treated by the investigator according to SOC." was added for use after the implementation of Protocol Amendment 4.	Clinical updates.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
15.	9.10 Biomarker, PK, Pharmacodynamic, and Pharmacogenomics, Samples	Indicated that with implementation of Protocol Amendment 4: -"…data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required for protocol purposes." -"BMA, [redacted] serum, and blood samples for biomarker, PK, pharmacodynamic and pharmacogenomic measurements will no longer be collected." -"…centralized clinical laboratory evaluations will no longer be performed." -"Local laboratory evaluations should be entered into the eCRF only if required to document a TEAE." - "For dosing decisions, response assessment, and all other safety assessments for the patient, local hematology and clinical chemistry laboratory results should be used and do not need to be entered into the eCRF." -"Local laboratory evaluations may be performed according to local SOC (ie, for acute management of TEAEs), per the investigator's judgment of SOC."	Clinical Updates.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
16.	9.10.1 Primary Specimen Collection for PK, Pharmacodynamic, and Biomarker Assessments 9.10.2 PK Measurements 9.10.3 [redacted] 9.10.3.1 [redacted] 9.10.3.2 [redacted] 9.10.4 [redacted] 9.10.5 Immunogenicity Sample Collection	"Upon implementation of Protocol Amendment 4 (see Section 1.3), BMA, [redacted], serum, and blood samples for biomarker, PK, pharmacodynamic and pharmacogenomic measurements will no longer be collected." was added for use after implementation of Protocol Amendment 4.	Clinical Updates.
17.	9.15 Posttreatment Follow-up Assessments	"Upon implementation of Protocol Amendment 4, patients will not be followed for the PFS or OS follow-up periods. See the SOE for appropriate assessments after the implementation of Protocol Amendment 4 in (Appendix A Table 1)." was added for use after implementation of Protocol Amendment 4.	Clinical Updates
18.	10.2 Procedures for Reporting and Recording AEs and SAEs 10.3 Monitoring AEs and Periods of Observation 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	"Upon implementation of Protocol Amendment 4, only SAEs (regardless of causality, including all deaths), any AE leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose) are to be reported." was added for use after implementation of Protocol Amendment 4.	Clinical Updates.

Property of Takeda. For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
19.	10.2 Procedures for Reporting and Recording AEs and SAEs	"Please note that while the types of AEs recorded and reported may differ dependent upon the implementation of Protocol Amendment 4, procedures for reporting AEs and SAEs will remain the same as stipulated here in Section 10.2."" was added for use after implementation of Protocol Amendment 4. SAE reporting contact information was added to match other protocols in the program.	Clarifications.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
20.	13.0 STATISTICAL METHODS 13.1 Statistical and Analytical Plans	Indicated that with implementation of Protocol Amendment 4: -"…activities will be limited to dosing of study drug and any modifications to administration and data collection requirements will be limited to the following safety assessments: all serious adverse events (SAEs) (regardless of causality, including all deaths), any adverse event (AE) leading to dose modification or discontinuation of study drug, Grade ≥3 AEs, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required." -"All central laboratory and investigator assessments of response and progression for protocol purposes are discontinued." -"Patients will not be followed for the progression-free survival (PFS) or overall survival (OS) follow-up periods, as PFS and OS will no longer be collected." -"Pharmacokinetic (PK) assessments will no longer be performed or recorded." -"Patients should otherwise be treated by the investigator according to local SOC. Local laboratory assessments should be performed per local SOC, and recording of AEs in the electronic case report form (eCRF) will be limited to AEs leading to dose modification or discontinuation of study drug."	Clinical updates.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v1 (Not Implemented)			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
21.	Appendix A Schedules of Events	Provided rationale for the implementation of the Updated Schedule of Events—Protocol Amendment 4 and Beyond. Added a new schedule of events for use with the implementation of Protocol Amendment 4 (Appendix A Table 1) and updated all other Schedules of Events for use prior to the implementation of Protocol Amendment 4 (Appendix A Table 2 through Appendix A Table 12). Updated the titles for the Schedules of Events (Appendix A Table 2 through Appendix A Table 12 to be used Prior to Protocol Amendment 4 with text indicating as such.	Clinical Updates
22.	Appendix B Bone Marrow Collection and Assessment Schedules	Provided text to indicate that "IMPORTANT NOTE: Bone marrow sample collection and assessment are no longer required as of the implementation of Protocol Amendment 4. Refer to Section 1.3 for a description of the changes to study conduct as a result of the implementation of Protocol Amendment 4."	Clinical updates and clarifications.
23.	Appendix C PK Sampling	Provided text to indicate that "IMPORTANT NOTE: Pharmacokinetic sample collection and assessment are no longer required as of the implementation of Protocol Amendment 4. Refer to Section 1.3 for a description of the changes to study conduct as a result of the implementation of Protocol Amendment 4."	Clinical updates and clarifications.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Protocol Amendment 4 v2 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 4 v2. The primary reason for this amendment was to implement new dose modification guidelines in cases of bleeding treatment-emergent adverse events (TEAEs) as an urgent safety measure to

mitigate the risk of fatal hemorrhagic events in response to the observation of a suspected unexpected serious adverse reaction (SUSAR) in the ongoing Study TAK-573-1501.

New dose modification guidelines have been added to this protocol.

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

Protocol Amendment 4 v2			
Summary of Changes Since the Last Implemented Version of the Approved Protocol			
Change Number	**Section(s) Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	8.2 Permitted Concomitant Medications and Procedures	Added "Platelet transfusion should not be applied only for the purpose of meeting the treatment criterion of platelet count to start a new cycle."	Updated to align with changes made in this protocol amendment.
2.	8.6.1.4 Criteria for Dose Interruption	Addition of Table 8.c with the dose modifications for modakafusp alfa bleeding TEAEs.	Updated to mitigate the risk of fatal hemorrhagic events.
3.	8.6.1.6 Criteria for Discontinuation	Removal of criteria related to Grade 4 life-threatening TEAEs.	Updated to align with changes made in this protocol amendment.
4.	8.7.1.2 Handling of Low Platelet Counts	Addition of mention to reference Table 8.c with the dose modifications for modakafusp alfa bleeding TEAEs	Updated to mitigate the risk of fatal hemorrhagic events.

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use

Signature Page for TAK-573-1502 Protocol Amend 05 US v1 2024-09-19
Title: Amend 05 US v1 to A Phase 1b Open-label Study to Evaluate the Safety and

Approval	[redacted] Clinical 25-Sep-2024 21:52:55 GMT+0000

Document Number: TDN-000443416 v1.0

Property of Takeda: For non-commercial use only and subject to the applicable Terms of Use