Clinical Study Protocol

NCT Number: NCT05590377

Title: A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed or Refractory Multiple Myeloma.

Study Number: TAK-573-2001

Document Version and Date: Amendment 2 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.

PROTOCOL

A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed or Refractory Multiple Myeloma

A Study of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed/Refractory Multiple Myeloma

Sponsor:	Takeda Development Center Americas, Inc 500 Kendall Street Cambridge, MA 02142 USA
Study Number:	TAK-573-2001
EudraCT Number:	2022-002169-14
Universal Trial Number:	Not applicable
Compound:	Modakafusp alfa (TAK-573)
Date:	19 September 2024 **Amendment Number:** 2 US v1

Amendment History:

Date	Amendment Number	Amendment Type	Region
19 September 2024	Amendment 2 US v1	Substantial; Regional	United States
03 April 2024	Amendment 1 v2	Substantial	Global
28 February 2024	Amendment 1 v1 (not implemented)	Substantial	Global
15 September 2023	Initial Protocol US v1	Nonsubstantial; Regional	United States
23 June 2023	Initial Protocol GB v1	Nonsubstantial; Regional	United Kingdom
05 April 2023	Initial Protocol DE v2	Nonsubstantial; Regional	Germany
05 April 2023	Initial Protocol DE v1	Nonsubstantial; Regional	Germany
27 January 2023	Initial Protocol CZ v1	Nonsubstantial; Regional	Czech Republic
14 December 2022	Initial Protocol FR v1	Nonsubstantial; Regional	France
16 August 2022	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Serious adverse event (SAE), pregnancy, and other applicable safety reporting information is presented in the study manual, as is information on reporting product complaints.

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

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

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 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]

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 patients 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 C).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 2 US v1 Summary of Changes

Protocol Amendment 2 US v1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 2 US v1. The primary reason for this amendment was to include the United States 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 G.

Protocol Amendment 2 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.	7.2 Exclusion Criteria	Added exclusion criterion #11: "Patient has a high risk of hemorrhage such as uncontrolled chronic bleeding disorder or is currently being treated with therapeutic anticoagulation."	Revised per FDA recommendation
2.	[redacted]	[redacted]	Revised per FDA recommendation

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

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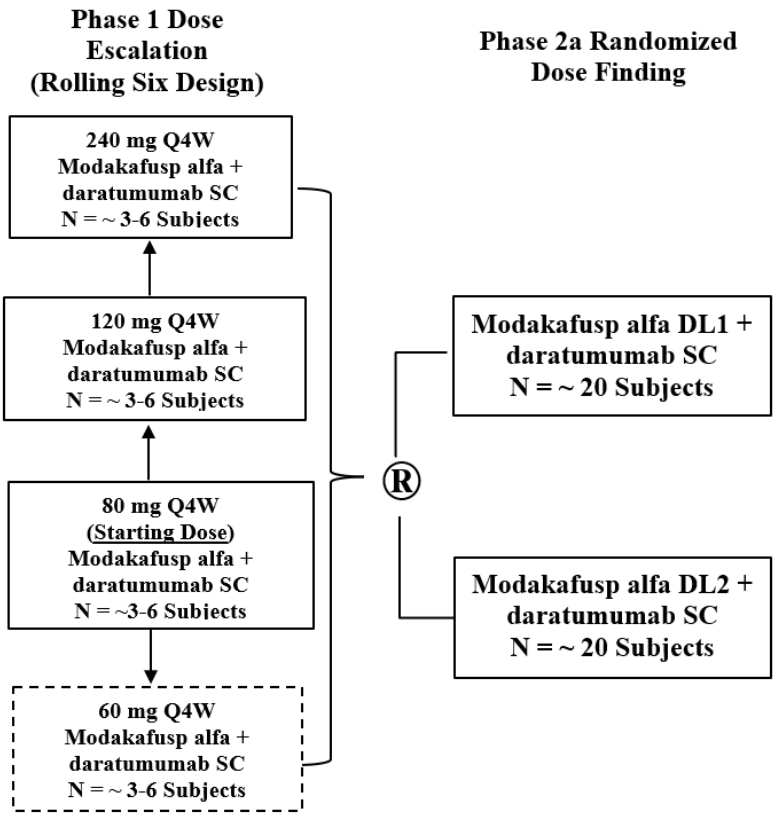
2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc	**Compound:** Modakafusp alfa (TAK-573)
Title of Protocol: A Phase 1/2a Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Modakafusp Alfa in Combination With Daratumumab Subcutaneous in Patients With Relapsed or Refractory Multiple Myeloma	**EudraCT No.:** 2022-002169-14
Study Number: TAK-573-2001	**Phase:** 1/2a
Study Design: This is a global multicenter, open-label, phase 1/2a study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of modakafusp alfa in combination with daratumumab subcutaneous (SC) in patients with relapsed or refractory multiple myeloma (RRMM). The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC. Two dose levels of modakafusp alfa in combination with daratumumab SC will be selected to be further explored in the randomized phase 2a dose finding part of the study. Patients will be randomized in a 1:1 ratio across 2 dose levels (DL1 or DL2) of modakafusp alfa in combination with daratumumab SC. The confirmed overall response rate (ORR) assessed by the investigator per International Myeloma Working Group (IMWG) criteria will be determined as the primary efficacy endpoint of the phase 2a dose finding. The optimized recommended phase 2 dose (RP2D) of modakafusp in combination with daratumumab SC will be selected on the basis of integrated safety, efficacy, PK, and PD data from the current study and other relevant stud(ies). A schematic of the study design is shown below.	



DL1: Dose Level 1; DL2: Dose Level 2; Q4W: every 4 weeks; R: randomization; SC: subcutaneous.

Phase 1 Dose Escalation

The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC during the Cycle 1 (28 days per cycle) dose-limiting toxicity (DLT) evaluation period and beyond. The proposed population in the phase 1 dose escalation will be patients with RRMM with at least 3 prior lines of therapy, including at least 1 proteasome inhibitor (PI), 1 immunomodulatory imide drug (IMiD), and 1 anti-CD38 monoclonal antibody (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) or therapy.

The dose escalation will follow the rolling six design with data collected in the dose escalation/de-escalation phase. Safety will be evaluated by the frequency of adverse events (AEs), severity, types of AEs, and by changes from baseline in patients' vital signs, weights, and clinical laboratory results.

The starting dose to be evaluated for modakafusp alfa will be 80 mg every 4 weeks (Q4W). Modakafusp alfa doses of 60, 120, or 240 mg Q4W could be evaluated depending on dose escalation/de-escalation rules specified by the rolling six design. Decision on dose escalation and de-escalation in phase 1 will be made on the basis of the number of patients in the current dose level, the number of patients experiencing DLTs, and the number of patients still at risk of developing a DLT at the time of a new patient entry. Three to 6 patients may concurrently be enrolled at a dose level in the study. The enrollment of the first 3 patients at the starting dose of 80 mg Q4W will be staggered by 24 hours each. The remaining patients can be dosed concurrently if there are no unexpected and significant acute toxicities. Accrual to the study may be paused while waiting for data from these 6 patients. Decisions as to whether to resume enrolling on the next dose level will be made using data available at the time of new patient enrollment. De-escalation will occur when 2 or more DLTs are observed at the current dose level,

whereas escalation will occur when 3 of 3, 4 of 4, 5 of 5, 5 of 6, or 6 of 6 patients are enrolled at the current dose level with no DLT observed and the next higher dose level has no more than 1 DLT observed. It is estimated that approximately 18 DLT-evaluable patients will be enrolled.

The daratumumab SC dose of 1800 mg (every week [QW] in Cycles 1 and 2, once every 2 weeks [Q2W] in Cycles 3 to 6, and Q4W thereafter) will be used in combination with modakafusp alfa throughout the study.

Phase 2a Dose Finding

Two dose levels of modakafusp alfa in combination with daratumumab SC doses will be selected from phase 1 dose escalation to be explored further in phase 2a open-label dose finding. Approximately 40 patients will be randomized 1:1 across 2 different dose levels (DL1 or DL2; N = 20 at each dose level) of modakafusp alfa in combination with daratumumab SC. Eligible patients will include patients with RRMM who have received 1 to 3 prior lines of therapy, refractory to lenalidomide, and sensitive (nonrefractory) or naive to anti-CD38 mAb. The randomization will be stratified by the number of prior lines of therapy (1 vs 2 or 3). The primary endpoint is the confirmed ORR assessed by the investigator per IMWG criteria.

Primary Objectives:

Phase 1 Dose Escalation

- To determine the safety and tolerability of modakafusp alfa in combination with daratumumab SC.

Phase 2a Dose Finding

- To inform the RP2D of modakafusp alfa in combination with daratumumab SC.
- To provide a preliminary evaluation of the clinical efficacy of modakafusp alfa in combination with daratumumab SC as measured by ORR.

Secondary Objectives:

Phase 1 Dose Escalation

- To characterize the PK profile of modakafusp alfa and daratumumab in the combination setting.
- To characterize antimyeloma activity as measured by ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- To characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.
- To characterize measurable (minimal) residual disease (MRD) negativity and duration of MRD negativity.

Phase 2a Dose Finding

- To determine DOR, clinical benefit rate (CBR), duration of clinical benefit (DCB), disease control rate (DCR), duration of disease control, time to progression (TTP), time to response (TTR), time to next treatment (TTNT), PFS, and OS.
- To further characterize safety and tolerability of modakafusp alfa in combination with daratumumab SC.
- To collect PK data for modakafusp alfa to support population PK and exposure-response analysis.
- To collect PK data for daratumumab SC to assess any potential impact of immunogenicity on daratumumab PK.
- To further characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.
- To characterize MRD negativity and duration of MRD negativity.

Patient Population: Patients aged 18 years or older with RRMM.

Number of Patients:	**Number of Sites:**
Phase 1 dose escalation: approximately 18 patients. Phase 2a dose finding: approximately 40 patients. A total of approximately 58 patients will be enrolled in this study.	Approximately 30 investigational centers globally.

Dose Level(s):	**Route of Administration:**
Modakafusp alfa: Phase 1 dose escalation: 60, 80 (starting dose), 120, or 240 mg Q4W in 28-day cycles. Phase 2a dose finding: 2 dose levels (DL1 and DL2) selected after the phase 1 dose escalation. Daratumumab SC: 1800 mg QW for Cycles 1 and 2, Q2W for Cycles 3 to 6, and Q4W thereafter in 28-day cycles.	Modakafusp alfa: Intravenous Daratumumab: SC
Duration of Treatment: Patients may receive study drug treatment until they experience progressive disease, unacceptable toxicity, or other discontinuation criteria are met.	**Period of Evaluation:** The study is expected to enroll patients for approximately 12 to 18 months (phase 1 and phase 2a) and continue follow-up for a total study duration of approximately 60 months.

Main Criteria for Inclusion:
Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Patients aged 18 years or older.
2. Documented MM diagnosis per IMWG criteria.
3. Measurable disease, defined as at least 1 of the following:
   a. Serum M protein ≥0.5 g/dL (≥5 g/L) on serum protein electrophoresis.
   b. Urine M protein ≥200 mg/24 hours on urine protein electrophoresis (UPEP).
   c. Serum free light chain (FLC) assay with involved FLC level ≥10 mg/dL (≥100 mg/L) provided serum FLC ratio is abnormal.
4. For patients in the phase 1 dose escalation only:
   Must have received at least 3 prior lines of 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) or therapy.
5. For patients in phase 2a dose finding only:
   a. Received 1 to 3 prior line(s) of antimyeloma therapy.
   b. Must be refractory to prior lenalidomide treatment.
   c. Patients must be sensitive (nonrefractory) or naïve to prior anti-CD38 mAb treatment.
   d. Documented progressive disease on or after the last regimen.
   e. Patients must have partial response (PR) or better to at least 1 line of prior therapy.

   Note:

   A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3 to 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 on therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease while on therapy.

Main Criteria for Exclusion:

1. Prior exposure to modakafusp alfa.
2. Patient has POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, plasma cell leukemia, or lymphoplasmacytic lymphoma.
3. Patient has not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5 Grade ≤1 or baseline, except for alopecia.
4. Previous allogeneic stem cell transplant at any time or autologous stem cell transplant within 12 weeks of planned start of dosing.
5. 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 to have minimal risk of recurrence within 3 years.

Endpoints:

Primary Endpoints:

Phase 1 Dose Escalation:

- DLT incidences.
- Frequency and severity of treatment-emergent adverse events (TEAEs) according to the NCI CTCAE, Version 5.0.

Phase 2a Dose Finding:

- ORR, defined as the proportion of patients who achieved a confirmed response of PR or better during the study as assessed by the investigator.

Secondary Endpoints:

Phase 1 Dose Escalation:

- Summary statistics by dose level and cycle day for the following PK parameters for modakafusp alfa for Cycles 1 and 2:
  - Single-dose maximum observed serum concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Apparent serum modakafusp alfa terminal disposition rate constant.
  - Apparent serum modakafusp alfa terminal disposition phase half-life.
  - Clearance.
  - Volume of distribution at steady state after intravenous administration.
- Summary statistics by dose level and cycle day for the following PK parameters for daratumumab for Cycles 1 and 2:
  - Single-dose C_{max}.
  - t_{max}.
  - Single-dose and multiple-dose observed concentration at the end of a dosing interval (C_{trough}).
  - AUC_{∞}.

- AUC_{last}.

- ORR by the investigator.
- DOR by the investigator.
- PFS by the investigator.
- OS.
- Antidrug antibody (ADA) incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).
- 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 negativity, at a threshold of 10^{-5}.

Phase 2a Dose Finding:

- DOR by investigator.
- CBR response of stringent complete response (sCR), CR, very good partial response (VGPR), PR, or minimal responses by investigator.
- DCB by investigator.
- DCR (CBR + stable disease) by investigator.
- Duration of disease control by investigator.
- TTP by investigator.
- TTR by investigator.
- TTNT.
- PFS by investigator.
- OS.
- Frequency and severity of TEAEs according to the NCI CTCAE, Version 5.0.
- ADA incidence and characteristics (eg, titer and specificity) and NAb.
- Rate of MRD[-] CR, at threshold of 10^{-5}, with CR assessed by the investigator.
- Rate of MRD[-], at a threshold of 10^{-5}.
- Duration of MRD negativity, at a threshold of 10^{-5}.

Statistical Considerations:

Phase 1 Dose Escalation

The dose escalation/de-escalation will be guided by the rolling six design. 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 population.

Phase 2a Dose Finding

The primary endpoint of phase 2a is ORR, which is defined as the percentage of patients with a confirmed PR or better (ie, PR, VGPR, CR, and sCR) according to the IMWG Response Criteria assessed by the investigator during the study. The observed ORR as well as associated 95% exact CI will be presented for each treatment arm. No formal statistical test will be performed to compare the 2 treatment arms.

Mean proportions and 2-sided 95% exact CIs will be presented for binary secondary endpoints, including CBR, DCR, rate of MRD[-] CR, and rate of MRD[-].

For secondary endpoints of DOR, DCB, duration of disease control, TTP, TTNT, PFS, OS, and duration of MRD negativity, Kaplan-Meier (K-M) survival curves and K-M medians (if estimable), together with 95% CIs, will be calculated for each arm.

For secondary endpoint of TTR, only responders are included in the analysis and it will be summarized as a continuous variable using mean TTR and 95% CI for each arm.

All disease responses or progression are assessed by the investigator per IMWG criteria.

Sample Size Justification:

A total of approximately 58 patients will be enrolled in the study, including approximately 18 DLT-evaluable patients for the phase 1 dose escalation and approximately 40 patients (approximately 20 patients per dose level) for the phase 2a dose finding.

The phase 1 dose escalation will accrue approximately 18 DLT-evaluable patients based on the algorithm of the rolling six design.

For phase 2a, approximately 20 patients per arm with a total of 40 patients will be enrolled. Patients who are randomized but do not receive any study treatment will be replaced. Patients enrolled for replacement purpose will be randomized. Patients who received at least 1 dose of any study treatment will be included in the analysis and will not be replaced if they drop out after receiving study treatment.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC_{∞}	area under the serum concentration-time curve from time 0 to infinity
AUC_{last}	area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration
BMA	bone marrow aspirate
CBR	clinical benefit rate
CFR	Code of Federal Regulations
C_{max}	maximum observed serum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
DCB	duration of clinical benefit
DCR	disease control rate
DL1	Dose Level 1
DL2	Dose Level 2
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eConsent	electronic consent
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
E-R	exposure-response
EU	European Union
FDA	[United States] Food and Drug Administration
FLC	free light chain
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
IB	investigator's brochure
ICF	informed consent form (including electronic consent where applicable)

Term	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon
IFN-α	interferon alpha
IFN-α2b	interferon alpha 2b
IMiD	immunomodulatory imide drug
IMWG	International Myeloma Working Group
IRB	institutional review board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
K-M	Kaplan-Meier
mAb	monoclonal antibody
MM	multiple myeloma
MOA	mechanism of action
MRD	measurable (minimal) residual disease
MRD[-]	MRD negative
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PO	orally
PR	partial response
PTA	posttrial access
QW	every week
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
RBC	red blood cells
RP2D	recommended phase 2 dose

Term	Definition
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SC	subcutaneous
sCR	stringent CR
SD	stable disease
SOE	Schedules of Event
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of maximum observed concentration
TTNT	time to next treatment
TTP	time to progression
TTR	time to response
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response

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

4.0 INTRODUCTION

4.1 Background

4.1.1 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 2016, the global incidence of MM increased by 126% (Cowan et al. 2018). The median age at diagnosis is 69 years with only 3.1% of patients younger than 45 years at diagnosis. It occurs slightly more frequently in men (8.8 per 100,000 men vs 5.9 per 100,000 women). MM incidence rate and mortality rate are approximately twice as common in the black and African American population compared with the white population (age-adjusted incidence rate and mortality rate of 13.8 per 100,000 persons and 6 per 100,000 persons, respectively, in the black and African American population compared with 6.5 per 100,000 persons and 3 per 100,000 persons, respectively, among the white population) (seer.cancer.gov/statfacts/html/mulmy.html, SEER Cancer Stat Facts: Myeloma, SEER 12. National Cancer Institute, Bethesda, MD, Accessed 02 June 2022). In the non-Hispanic black population, the incidence of MM was 17 per 100,000 men and 12.9 per 100,000 women; in the non-Hispanic white population, the incidence of MM was 8.1 per 100,000 men and 5.0 per 100,000 women. This racial disparity is related to the higher prevalence of monoclonal gammopathy of undetermined significance in black and African American populations (Rajkumar and Kumar 2016).

From 2010 to 2016, the 5-year survival rate of patients with MM was approximately 53.9% (themmrf.org/multiple-myeloma/prognosis/understanding-survival-statistics, Relative Survival for Multiple Myeloma, Accessed 19 May 2022). 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 has improved in the last decade with the discovery, development, and approval of proteasome inhibitors (PIs) (eg, bortezomib) and immunomodulatory imide 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 small molecular or biologic agents with newer mechanisms of action (MOAs), such as anti-CD38 monoclonal antibody (mAb) drugs including daratumumab and isatuximab (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022; Sarclisa (Isatuximab) 2020), selinexor (selective inhibitor of nuclear export) (Xpovio (selinexor) tablets for oral use 2021), belantamab mafodotin (BCMA [B-cell maturation antigen]–targeting antibody drug conjugate) (Blenrep (belantamab mafodotin-blmf) 2020), idecabtagene vicleucel and ciltacabtagene autoleucel (chimeric antigen receptor T-cell therapies) (Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021; Carvykti (ciltacabtagene autoleucel) Suspension for Intravenous Infusion 2022). Despite these recent advances, these are not curative therapies and there is still a

need for the development of novel targeted therapies that are safe and efficacious against MM cells.

While these new therapies are promising, improved treatment options for patients refractory to lenalidomide are needed. Efficacy results from phase 3 studies of novel combinations in patients refractory to lenalidomide are limited, as these patients are often under-represented in randomized trials. Furthermore, most of the treatment combinations that are currently approved to treat patients with relapsed or refractory multiple myeloma (RRMM) have lenalidomide in their regimen. Despite recently approved CD38 mAb combinations (ie, daratumumab subcutaneous [SC], bortezomib, and dexamethasone and daratumumab SC, pomalidomide, and dexamethasone), which do not include lenalidomide, the clinical outcomes for patients refractory to lenalidomide treated with novel combination therapies remain unsatisfactory, with lower responses and progression-free survival (PFS) compared with patients sensitive to lenalidomide (Richard et al. 2021). There is still a need for the development of novel targeted therapies that are efficacious and well-tolerated that may overcome certain limitations of current therapies.

4.1.2 Modakafusp Alfa

Modakafusp alfa, previously known as TAK-573, is a novel, first-in-class immune targeting attenuated cytokine that delivers interferon alpha 2b (IFN-α2b) to immune cells. Modakafusp alfa consists of 2 IFN-α2b molecules that are genetically fused to the Fc portion of a humanized IgG4 anti-CD38 mAb. Modakafusp alfa binds noncompetitively to a different epitope on CD38 than other commercially available anti-CD38 antibodies. The IFN-α2b molecules of modakafusp alfa are attenuated, leading to reduced interferon (IFN) receptor binding affinity, thereby driving targeted delivery of interferon alpha (IFN-α) to CD38 expressing cells. Because CD38 is expressed on a variety of immune cells, modakafusp alfa can promote broad innate and adaptive immune stimulation through activation of the IFN-α receptor pathway. Additionally, modakafusp alfa demonstrated direct antiproliferative effects on CD38 expressing MM plasma cells in nonclinical studies.

4.1.2.1 Nonclinical Studies

Pharmacokinetic (PK) and toxicokinetic data were generated in nonclinical pharmacology and toxicology studies, and safety pharmacology endpoints were included in the 29-day repeat dose Good Laboratory Practice compliant toxicology study in cynomolgus monkeys. Detailed nonclinical information is provided in the IB. Nonclinical pharmacology data were also generated in support of Study TAK-573-2001. An in vivo nonclinical study was conducted with modakafusp alfa in combination with daratumumab (modakafusp alfa + daratumumab) in a nonclinical NCI H929 xenograft model, demonstrating a significant reduction of the median tumor volume when compared with either single agent alone. Combination toxicity studies were not performed in accordance with ICH S9.

4.1.2.2 Clinical Studies

Clinical studies are ongoing with modakafusp alfa as a single agent in adult patients with RRMM (Study TAK-573-1501), with modakafusp alfa as part of combination therapy in adult patients

with newly diagnosed multiple myeloma (NDMM) in maintenance after autologous stem cell transplant (ASCT) or RRMM (Study TAK-573-1502), 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-573-1501

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", as of the data cutoff date of 23 January 2022 has enrolled 95 subjects.

This study is being conducted in 3 parts: Part 1 is modakafusp alfa single agent dose escalation, Part 2 is single agent dose expansion, and Part 3 is designed as an extension study to assess safety and efficacy in patients with RRMM after modakafusp alfa single agent treatment with 120 mg or 240 mg once every 4 weeks (Q4W) dosing. The phase 1 single agent portion of the study followed a 3 + 3 dose escalation design to determine a maximum tolerated dose (MTD) or an optimal biologic dose.

Part 1 of Study TAK-573-1501 was to evaluate the safety and tolerability of modakafusp alfa single agent in patients with RRMM. It involved extensive dose escalation with 10 dose levels of modakafusp alfa (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 Q4W on the basis of the recovery time of hematological toxicities. The MTD at this schedule was established as 3 mg/kg Q4W, because 6 mg/kg Q4W exceeded the MTD with 2 dose-limiting toxicities (DLTs) (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 Q4W. 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 conducted with 1 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 (PD) endpoints; up to 25 patients are planned to be enrolled in this cohort.

As of 23 January 2022, 39 patients have been enrolled in the Part 2 dose expansion phase, with 25 of these patients receiving 1.5 mg/kg Q4W. Of the additional patients in Part 2 expansion cohorts, 8 received 0.4 mg/kg once every 3 weeks (Q3W), 3 received 0.4 mg/kg Q3W + dexamethasone, and 3 received 1.5 mg/kg Q4W + dexamethasone. In the expansion cohort receiving 1.5 mg/kg Q4W (N = 25), the overall response rate (ORR) was 48% and the median duration of response (DOR) has not yet been reached. Since the data cutoff of 23 January

2022, an additional 5 patients have been enrolled to the expansion cohort of 1.5 mg/kg Q4W + dexamethasone.

In the 1.5 mg/kg Q4W treatment group (N = 30) with pooled data from the Part 1 dose escalation and Part 2 dose expansion, toxicities were primarily hematologic, with thrombocytopenia and neutropenia observed at rates of 73.3% (16.7% Grade 4) and 70.0% (30.0% Grade 4), respectively. IRRs have been observed at a rate of 33.3%, with only 1 event (3.3%) being 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 the available data by May 2022, 13% of the immunogenicity-evaluable patients (ie, patients with antidrug antibodies [ADAs]) evaluated at baseline and at least 1 posttreatment visit, N = 90) reported positive ADA at baseline. Fifty-four percent of the immunogenicity-evaluable patients reported positive ADA posttreatment.

No dose response on the ADA incidence and titer have been observed. The first incidence of posttreatment ADA formation was reported as early as Cycle 1 Day 15 (earliest posttreatment sampling), and most ADA appeared to be persistent. The potential impact of ADAs on PK, PD efficacy, and safety will be further evaluated in the study.

Lastly, integrated dose-response and exposure-response (E-R) relationships based on efficacy and safety data indicate that 1.5 and 3 mg/kg Q4W dosing are within the optimal biological dose range.

Based on holistic evaluations of the data (efficacy, safety, exposure, immunogenicity, E-R, etc), and to further assess the optimal dose, a randomized noncomparative Part 3 of the study is being conducted to evaluate modakafusp alfa 120 mg or 240 mg Q4W (the fixed dosing equivalents of 1.5 and 3 mg/kg, respectively). Part 3 aims to compare the efficacy and safety between 120 and 240 mg Q4W to establish the dose with an optimal benefit-risk profile.

TAK-573-1502

Study TAK-573-1502, “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”, is a planned study in patients with NDMM in maintenance posttransplant or RRMM assessing the safety of the combination of modakafusp alfa with different standard of care agents for MM. Clinical safety or efficacy data is not yet available from this study.

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 Q3W.

The study consists of 2 phases. The phase 1b dose escalation portion of the study, which enrolled patients with advanced/metastatic solid tumors, was designed to determine the single-agent recommended phase 2 dose (RP2D) and schedule of modakafusp alfa. The phase 2 expansion portion will assess the efficacy of modakafusp alfa in combination with pembrolizumab in patients with unresectable/metastatic melanoma. The phase 2 expansion will begin with a safety lead-in to evaluate safety and tolerability of the combination.

As of the data cutoff of 23 November 2021, a total of 2 DLTs were identified across all dose levels being tested in the phase 1b single-agent dose escalation; both DLTs were at 1.5 mg/kg Q3W, 1 of Grade 4 thrombocytopenia, and the other a Grade 3 confusion. The single-agent 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 pharmacologically active dose range was determined to be 0.1 to 1.5 mg/kg Q3W.

Based on the available data of September 2021, 12% of patients at baseline and 100% of patients posttreatment who were immunogenicity-evaluable (N = 17) with solid tumors reported positive ADA. No dose response on the ADA incidence and titer has been observed. The first incidence of posttreatment ADA formation was reported as early as Cycle 2 Day 1 (earliest posttreatment sampling), and both transient and persistent ADAs were observed. The potential impact of ADAs on PK, PD efficacy, and safety will be further evaluated in the study.

4.1.3 Combination Agent

4.1.3.1 Daratumumab SC

Study TAK-573-2001 will investigate modakafusp alfa in combination with daratumumab SC. Daratumumab is an immunoglobulin G1 kappa human mAb that binds to CD38 antigens and inhibits the growth of CD38-expressing tumor cells by inducing apoptosis directly through Fc-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 and hyaluronidase for SC administration. It is approved as monotherapy and in combination with standard antimyeloma therapies for adult patients with MM (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022).

In patients with NDMM, daratumumab SC is approved in the United States (US) and the European Union (EU) in combination with bortezomib/melphalan/prednisone; in combination with lenalidomide/dexamethasone; or in combination with bortezomib/thalidomide/dexamethasone. In patients with RRMM, in US and EU daratumumab SC is approved in combination with bortezomib/dexamethasone or pomalidomide/dexamethasone in patients who have received at least 1 prior therapy. In patients with RRMM, daratumumab SC is also approved in the US and EU in combination with lenalidomide and dexamethasone in patients who have received at least 1 prior therapy. Daratumumab SC is also indicated as monotherapy in the US and EU in patients who have

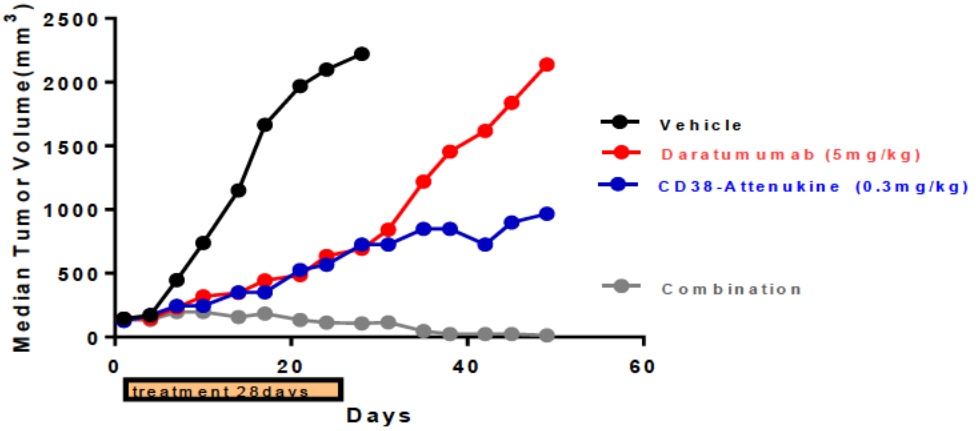
received a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

4.2 Rationale for the Proposed Study

4.2.1 Modakafusp Alfa in Combination With Daratumumab SC

Modakafusp alfa has both an epitope binding site on CD38 and an MOA, that are distinct from the commercially available anti-CD38 mAbs, daratumumab and isatuximab. Anti-CD38 mAbs mechanisms are driven through IgG1 Fc effector functionality, while modakafusp alfa's mechanism is driven through induced IFN signaling within the CD38 expressing cells. Given the broad expression of CD38 on many immune cells, IFN signaling has been shown to induce both innate and adaptive immune cell activation as well as elicit antiproliferative and/or apoptotic effects within the myeloma tumor cells. Given the different, potentially complementary MOA, modakafusp alfa, at the sensitive dose, and daratumumab were combined in a nonclinical NCI-H929 xenograft model, which demonstrated a significant reduction of the median tumor volume when compared with either single agent alone (Figure 4.a). Because CD38 is an IFN-responsive gene, expression was evaluated both nonclinically and clinically after modakafusp alfa treatment, which showed an increase of CD38 expression of 2- to 3-fold on the surface of immune cells (Collins et al. 2020). In the context of the combination of modakafusp alfa and daratumumab, this increase in CD38 expression induced by modakafusp alfa could counteract the downregulation of CD38 typically seen with anti-CD38 mAbs (Vogl et al. 2021). In Study TAK-573-1501 (NCT03215030), a clinical study evaluating single-agent activity of modakafusp alfa in an RRMM patient population, modakafusp alfa has shown promising antimyeloma activity in heavily pretreated patients, including patients refractory to anti-CD38 mAbs and those who have received an anti-CD38 mAb in their most recent line of treatment (N = 3).

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



Source: Report H929-e324.

BIW: twice weekly; IP: intraperitoneally.

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.

4.2.2 Study Population

The proposed population in the phase 1 dose escalation will be patients with RRMM with at least 3 prior lines of 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) or therapy. Given that the safety and tolerability of modakafusp alfa in combination with daratumumab SC has not been previously established, it is appropriate to initially test this novel combination therapy in patients with RRMM with a high unmet medical need. Modakafusp alfa monotherapy has shown promising antimyeloma activity in heavily pretreated patients, including patients refractory to anti-CD38 mAbs and those who had received an anti-CD38 mAb in their most recent line of treatment.

The population in phase 2a dose finding will be patients with RRMM after 1 to 3 prior lines of therapy who are refractory to lenalidomide and sensitive (nonrefractory) or naive to anti-CD38 mAb. This population represents the target population for the future registrational study.

4.3 Modakafusp Alfa Starting Dose Justification for the Phase 1 Dose Escalation in Combination With Daratumumab SC

The initial dose level to be evaluated for modakafusp alfa in the phase 1 dose escalation in combination with daratumumab SC will be 80 mg Q4W, which is N-1 or N-2 of the potential modakafusp alfa single agent doses of 120 mg or 240 mg Q4W, respectively, which are currently being assessed in Part 3 of Study TAK-573-1501 for selection of an optimal single agent dose. The dosing of daratumumab SC will be 1800 mg every week (QW) for Cycles 1 and 2, once

every 2 weeks (Q2W) for Cycles 3 to 6, and Q4W thereafter in 28-day cycles (see Section 8.1.2 for additional dosing information).

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

On the basis of the single-agent safety profile of modakafusp alfa from Study TAK-573-1501 described in Section 4.1.2.2, the major potential overlapping toxicities anticipated with modakafusp alfa in combination with daratumumab SC are thrombocytopenia and neutropenia, with the possible clinical manifestation of bleeding and infection. As such, these clinical events were analyzed in patients treated with modakafusp alfa (Study TAK-573-1501) at the body weight-based Q3W and Q4W dosing schedule equivalent to flat dose of 70 to 90 mg. Only 1 of 10 patients in this group reported a treatment-emergent adverse event (TEAE) within the System Organ Class of infections and infestations, which was an event of oral herpes. This event was assessed as Grade 2 and unrelated to modakafusp alfa. There was 1 TEAE of Grade 1 epistaxis which was assessed as unrelated to modakafusp alfa.

In addition, in the same 10 patients treated with equivalent flat dose of 70 to 90 mg, ORR responses were observed in 3 of 10 patients (30%). Clinical efficacy at doses <70 mg was very limited, with 1 of 19 patients (5%) with a reported response.

On the basis of the anticipated 3- to 6-fold reduction in median single-dose AUC at 80 mg Q4W of modakafusp alfa versus 120 mg or 240 mg Q4W, and safety and clinical efficacy profiles observed at 70 to 90 mg Q3W and Q4W from a modakafusp alfa single-agent study, 80 mg Q4W would be an appropriate starting dose in combination with daratumumab SC for the phase 1 dose escalation. In addition, intensive safety monitoring including rigorous chemistry and hematologic assessments will be included in the initial cycles of the current study. This will enable close monitoring of TEAEs for prompt medical interventions if needed.

4.4 Modakafusp Alfa Dose Selection for Phase 2a Dose Finding in Combination With Daratumumab SC

After the phase 1 dose escalation of modakafusp alfa in combination with daratumumab SC is completed, 2 modakafusp alfa dose levels will be selected for the 1:1 randomized phase 2a dose finding in combination with daratumumab SC.

The selection of 2 dose levels of modakafusp alfa in combination with daratumumab SC for the phase 2a dose finding will be made on the basis of the overall assessment of the results from the following:

1. The rolling six recommended tolerable doses in the phase 1 dose escalation based on DLT data in Cycle 1.
2. Additional safety, tolerability, PK, and PD data as available from Cycle 1 and beyond in the phase 1 dose escalation.

3. The benefit-risk assessment for 120 mg Q4W and 240 mg Q4W based on emerging efficacy and safety data from the phase 2, Part 3 extension of the separate ongoing modakafusp alfa monotherapy study (Study TAK-573-1501).

Therefore, integrated PK, PD, efficacy, and safety data analyses will be conducted using the phase 1 dose escalation data in combination with daratumumab SC and single-agent data from Study TAK-573-1501, Part 3 extension to select the 2 dose levels of modakafusp alfa in combination with daratumumab SC in the phase 2 dose finding.

4.5 Risks and Benefits

4.5.1 Modakafusp Alfa

Modakafusp alfa has been administered to over 100 patients with MM and solid tumors in ongoing studies (see Study TAK-573-1501 and Study TAK-573-1001 in Section 4.1.2.2).

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 central nervous system, 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

As of 23 January 2022 in the single-agent study in patients with RRMM, Study TAK-573-1501 (N = 95), the most common nonhematologic TEAEs were hyperglycaemia (33.7%), fatigue (32.6%), hypocalcaemia (23.2%), and hyponatraemia (22.1%). The most common TEAEs Grade ≥3 were hematologic: neutropenia (52.6%), thrombocytopenia (49.5%), leukopenia (37.9%), and anemia (29.5%). Infections were uncommon, with pneumonia occurring in 8 patients (8.4%) and upper respiratory tract infection in 6 patients (6.3%). Two patients (2.1%) had TEAEs of febrile neutropenia.

Hematologic Toxicities

The most common TEAEs reported have been hematologic. Overall, these hematologic TEAEs were thrombocytopenia (including platelet count decreased) (77.9%), followed by neutropenia (including neutrophil count decreased) (58.9%), anaemia (56.8%), leukopenia (52.6%), and

lymphocyte count decreased (38.9%). The majority of patients (85.3%) had a TEAE related to study drug; the most frequently reported TEAEs related to study drug were hematologic, including thrombocytopenia (64.2%), neutropenia (49.5%), and leukopenia (44.2%). Two patients (2.1%) had Grade ≥3 TEAEs of febrile neutropenia. Grade ≥3 hematologic TEAEs included neutropenia (52.6%), thrombocytopenia (49.5%), leukopenia (37.9%), anaemia (29.5%), and lymphocyte count decreased (27.4%).

Hematologic TEAEs leading to any dose modification were thrombocytopenia 15 (15.8%), leukopenia 2 (2.1%), anemia 2 (2.1%). The hematologic TEAEs leading to discontinuation of study drug were thrombocytopenia 2 (2.1%), disseminated intravascular coagulation 1 (1.1%) and neutropenia 1 (1.1%).

With 1.5 mg/kg Q4W, mean platelet counts and absolute neutrophil count (ANC) were lowest at Day 8 or 15 of the first 2 cycles and recovered sufficiently to continue dosing in the next cycle without dosing delay in most cases.

IRRs

Patients receiving modakafusp alfa have experienced IRRs. In Study TAK-573-1501 (patients with RRMM), 18 patients (18.9%) experienced an IRR, 2 (2.1%) of which were Grade ≥3 and 3 (3.2%) of which were SAEs. Four patients (4.2%) required a dose modification due to an IRR.

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 mandatory that all patients receive premedication before modakafusp alfa dosing unless contraindicated (see Section 8.1.1.3).

It is important to monitor for signs and symptoms of IRRs and treat accordingly. Resuscitation medications and equipment should be available before, during, and after the infusion. Premedications and treatment should be provided as described in Section 8.1.1.3.

Other

Neuropsychiatric events have been reported in modakafusp alfa clinical studies. In Study TAK-573-1501, overall (N = 95) there were 9 TEAEs (9.5%) of insomnia, 5 TEAEs (5.3%) of confusional state, 4 TEAEs (4.2%) each of agitation and depression, 2 TEAEs (2.1%) each of encephalopathy and mental status changes, and 1 TEAE (1.1%) each of anxiety and restlessness. Grade 3 and higher neuropsychiatric events were encephalopathy 2 (2.1%), spinal cord compression 2 (2.1%), syncope 1 (1.1%), mental status changes 1 (1.1%), and confusional state 1 (1.1%). Of these, the events assessed as serious were encephalopathy 2 (2.1%), spinal cord compression 2 (2.1%), confusional state 1 (1.1%), and mental status changes 1 (1.1%).

Some patients receiving modakafusp alfa have experienced elevation in liver enzymes. In Study TAK-573-1501, TEAEs of aspartate aminotransferase (AST) increased and alanine

aminotransferase (ALT) increased were observed in 18.9% and 14.7% of patients, respectively. One TEAE each of AST and ALT increased were Grade ≥3; however, none were SAEs.

Modakafusp alfa elicited a low level of cytokine release (tumor necrosis factor alpha, IL-6, IL-8, interferon gamma, and IL-2) from human peripheral blood mononuclear cells 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. One TEAE of CRS Grade 2 was reported in Study TAK-573-1001 in solid tumors; this TEAE was considered to be related to the study drug.

For more detailed information on the adverse events (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) located in Appendix A. Dose modification should be applied per the guidelines in Section 8.6.

Further details for modakafusp alfa administration, safety events, and management can be found in Section 8.0 and the Guidance for Investigator section of the IB.

4.5.2 Combination Agent

4.5.2.1 Combination Agent Daratumumab SC

The most frequently reported adverse reactions associated with daratumumab SC monotherapy (incidence ≥20%) is upper respiratory infection. The most common (≥40%) hematology laboratory abnormalities with daratumumab SC are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin. Refer to daratumumab and hyaluronidase-fihj Prescribing Information for more details (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022).

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).

Interference with serological testing has been described with the anti-CD38 antibody daratumumab, which binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). A daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rhesus factor blood type are not impacted (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022). Therefore, blood transfusion centers should be notified of this interference with serological testing, and patients should be typed and screened before starting daratumumab SC if not performed previously.

The main overlapping toxicities expected with modakafusp alfa and daratumumab SC, on the basis of the single-agent profile of both drugs are neutropenia, and thrombocytopenia (Mateos et al. 2020; Vogl et al. 2021). Hematologic AEs (eg, neutropenia and thrombocytopenia) will be managed with dose delays, growth factors, and platelet transfusion, if needed. Both modakafusp alfa and daratumumab SC were reported with IRRs but with only 2.1% and 1% at Grade 3 for each agent, respectively. IRRs will be proactively managed with premedication and careful patient monitoring after infusion.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

Phase 1 Dose Escalation

- To determine the safety and tolerability of modakafusp alfa in combination with daratumumab SC.

Phase 2a Dose Finding

- To inform the RP2D of modakafusp alfa in combination with daratumumab SC.
- To provide a preliminary evaluation of the clinical efficacy of modakafusp alfa in combination with daratumumab SC as measured by ORR.

5.1.2 Secondary Objectives

Phase 1 Dose Escalation

- To characterize the PK profile of modakafusp alfa and daratumumab in the combination setting.
- To characterize antimyeloma activity as measured by ORR, DOR, PFS, and overall survival (OS).
- To characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.
- To characterize measurable (minimal) residual disease (MRD) negativity and duration of MRD negativity.

Phase 2a Dose Finding

- To determine DOR, clinical benefit rate (CBR), duration of clinical benefit (DCB), disease control rate (DCR), duration of disease control, time to progression (TTP), time to response (TTR), time to next treatment (TTNT), PFS, and OS.
- To further characterize safety and tolerability of modakafusp alfa in combination with daratumumab SC.
- To collect PK data for modakafusp alfa to support population PK and E-R analysis.
- To collect PK data for daratumumab SC to assess any potential impact of immunogenicity on daratumumab PK.
- To further characterize the immunogenicity of modakafusp alfa in combination with daratumumab SC.

- To characterize MRD negativity and duration of MRD negativity.

5.1.3 Exploratory Objectives

[redacted]

5.2 Endpoints

Patients' responses to the treatment will be determined per International Myeloma Working Group (IMWG) criteria in the current study.

5.2.1 Primary Endpoints

The primary endpoints are:

Phase 1 Dose Escalation

- DLT incidences (see Section 8.3.1).
- Frequency and severity of TEAEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

Phase 2a Dose Finding

- ORR, defined as the proportion of patients who achieved a confirmed response of PR or better during the study as assessed by the investigator.

5.2.2 Secondary Endpoints

The secondary endpoints are:

Phase 1 Dose Escalation

- Summary statistics by dose level and cycle day for the following PK parameters for modakafusp alfa for Cycles 1 and 2:
  - Single-dose maximum observed serum concentration (C_{max}).
  - Time of first occurrence of C_{max} (t_{max}).
  - Area under the serum concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - Apparent serum modakafusp alfa terminal disposition rate constant.
  - Apparent serum modakafusp alfa terminal disposition phase half-life.
  - Clearance.
  - Volume of distribution at steady state after intravenous (IV) administration.

- Summary statistics by dose level and cycle day for the following PK parameters for daratumumab for Cycles 1 and 2:
  - Single-dose C_{max}.
  - t_{max}.
  - Single-dose and multiple-dose observed concentration at the end of a dosing interval (C_{trough}).
  - AUC_{∞}.
  - AUC_{last}.
- ORR by the investigator.
- DOR by the investigator.
- PFS by the investigator.
- OS.
- ADA incidence and characteristics (eg, titer and specificity) and neutralizing antibody (NAb).
- 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 negativity, at a threshold of 10^{-5}.

<u>Phase 2a Dose Finding</u>

- DOR by investigator.
- CBR response of sCR, CR, very good partial response (VGPR), PR, or minimal responses by investigator.
- DCB by investigator.
- DCR (CBR + stable disease [SD]) by investigator.
- Duration of disease control by investigator.
- TTP by investigator.
- TTR by investigator.
- TTNT.
- PFS by investigator.
- OS.
- Frequency and severity of TEAEs according to the NCI CTCAE, Version 5.0.

- ADA incidence and characteristics (eg, titer and specificity) and NAb.
- Rate of MRD[-] CR, at threshold of 10^{-5}, with CR assessed by the investigator.
- Rate of MRD[-], at a threshold of 10^{-5}.
- Duration of MRD negativity, at a threshold of 10^{-5}.

5.2.3 Exploratory Endpoints

[redacted]

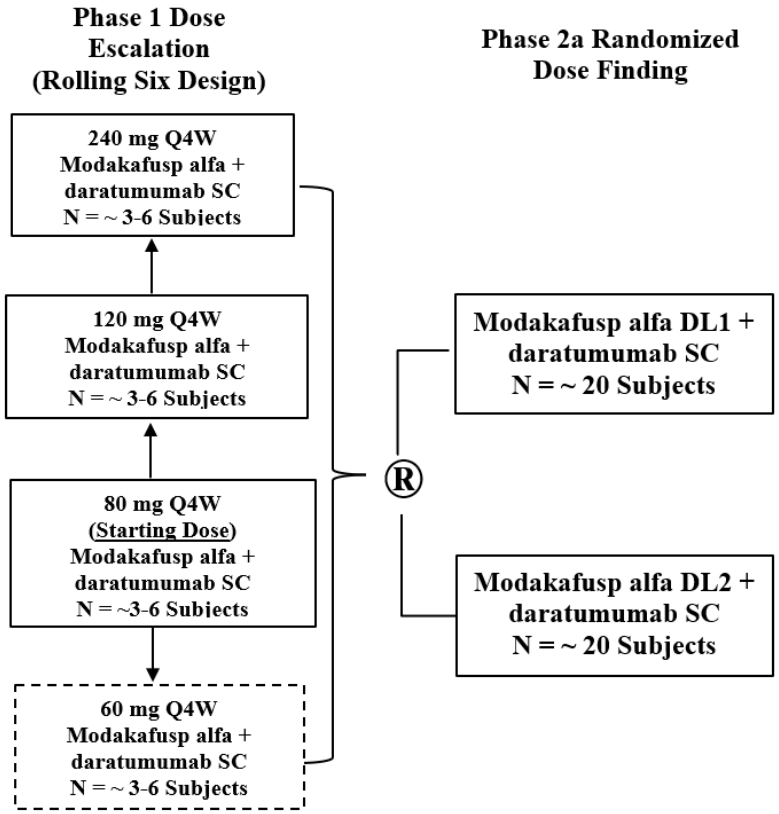
6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a global multicenter, open-label, phase 1/2a study designed to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of modakafusp alfa in combination with daratumumab SC in patients with RRMM. The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC. Two dose levels of modakafusp alfa in combination with daratumumab SC will be selected to be further explored in the randomized phase 2a dose finding part of the study (see Section 4.4). Patients will be randomized in a 1:1 ratio across 2 dose levels (DL1 or DL2) of modakafusp alfa in combination with daratumumab SC. The confirmed ORR assessed by the investigator per IMWG criteria will be determined as the primary efficacy endpoint of the phase 2a dose finding. The optimized RP2D of modakafusp in combination with daratumumab SC will be selected on the basis of integrated safety, efficacy, PK, and PD data from the current study and other relevant stud(ies) (eg, Study TAK-573-1501).

A schematic of the study design is included as Figure 6.a. SOEs are provided in Appendix A.

Figure 6.a Schematic of TAK-573-2001 Study Design



DL1: Dose Level 1; DL2: Dose Level 2; Q4W: every 4 weeks; R: randomization; SC: subcutaneous.

Phase 1 Dose Escalation

The study will begin with a phase 1 dose escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC during the Cycle 1 (28 days per cycle) DLT evaluation period and beyond. The proposed population in the phase 1 dose escalation will be patients with RRMM with at least 3 prior lines of 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) or therapy.

The dose escalation will follow the rolling six design (Skolnik et al. 2008) with data collected in the dose escalation/de-escalation phase. Safety will be evaluated by the frequency of AEs, severity, types of AEs, and by changes from baseline in patients' vital signs, weights, and clinical laboratory results.

The starting dose to be evaluated for modakafusp alfa will be 80 mg Q4W (Section 4.3). Modakafusp alfa doses of 60, 120, or 240 mg Q4W could be evaluated depending on dose escalation/de-escalation rules specified by the rolling six design. Decision on dose escalation and de-escalation in phase 1 will be made on the basis of the number of patients in the current dose level, the number of patients experiencing DLTs, and the number of patients still at risk of developing a DLT at the time of a new patient entry. Three to 6 patients may concurrently be enrolled at a dose level in the study. The enrollment of the first 3 patients at the starting dose of 80 mg Q4W will be staggered by 24 hours each. The remaining patients can be dosed concurrently if there are no unexpected and significant acute toxicities. Accrual to the study may be paused while waiting for data from these 6 patients. Decisions as to whether to resume enrolling on the next dose level will be made using data available at the time of new patient enrollment (see Section 8.4 and Table 8.a for more details). De-escalation will occur when 2 or more DLTs are observed at the current dose level, whereas escalation will occur when 3 of 3, 4 of 4, 5 of 5, 5 of 6, or 6 of 6 patients are enrolled at the current dose level with no DLT observed and the next higher dose level has no more than 1 DLT observed. It is estimated that approximately 18 DLT-evaluable patients will be enrolled.

The daratumumab SC dose of 1800 mg (QW in Cycles 1 and 2, Q2W in Cycles 3 to 6, and Q4W thereafter) will be used in combination with modakafusp alfa throughout the study.

Phase 2a Dose Finding

Two dose levels of modakafusp alfa in combination with daratumumab SC doses will be selected from phase 1 dose escalation to be explored further in phase 2a open-label dose finding. Approximately 40 patients will be randomized 1:1 across 2 different dose levels (DL1 or DL2; N = 20 at each dose level) of modakafusp alfa in combination with daratumumab SC. Eligible patients will include patients with RRMM who have received 1 to 3 prior lines of therapy, refractory to lenalidomide, and sensitive (nonrefractory) or naive to anti-CD38 mAb. The randomization will be stratified by the number of prior lines of therapy (1 vs 2 or 3). The primary endpoint is the confirmed ORR assessed by the investigator per IMWG criteria.

6.2 Number of Patients

A total of approximately 58 patients will be enrolled in this study at approximately 30 study centers globally.

6.2.1 Phase 1 Dose Escalation

Approximately 18 patients will be enrolled in the phase 1 dose escalation/de-escalation. During phase 1, patients who are determined as DLT non-evaluable will be replaced. The definition of DLT-evaluable patients is provided in Section 13.1.1.

6.2.2 Phase 2a Dose Finding

Approximately 40 patients (approximately 20 patients per arm) will be enrolled in the phase 2a dosing-finding study.

Patients who are randomized but do not receive any study treatment will be replaced. Patients enrolled for replacement purpose will be randomized. Patients who received at least 1 dose of any study treatment will be included in the analysis and will not be replaced if they drop out after receiving study treatment.

The definition of evaluable patients and determination of sample size are provided in Section 13.0.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive study drug treatment until they experience progressive disease, unacceptable toxicity, or other discontinuation criteria are met.

Patients who discontinue study drug treatment for reasons other than progressive disease will continue PFS follow-up every 4 weeks from the end of treatment (EOT) visit until the occurrence of progressive disease, death, the start of subsequent systemic antineoplastic therapy, study termination, whichever occurs first. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

6.3.2 End of Study/Study Completion Definition 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.

Should the study be closed prematurely, the site will no longer be able to access the 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 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.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Phase 1 Dose Escalation		
Primary: DLT incidences	Section 8.3.1	Up to 60 months
Primary: Frequency and severity of TEAEs	Section 13.1.8	Up to 60 months
Secondary: Summary PK statistics for modakafusp alfa in Cycles 1 and 2	Sections 5.2.2 and 13.1.4	Up to 60 months
Secondary: Summary PK statistics for daratumumab in Cycles 1 and 2	Sections 5.2.2 and 13.1.4	Up to 60 months
Secondary: ORR by investigator	Section 13.1.3.1	Up to 60 months
Secondary: DOR by investigator	Section 13.1.3.2.1	Up to 60 months
Secondary: PFS by investigator	Section 13.1.3.2.1	Up to 60 months
Secondary: OS	Section 13.1.3.2.1	Up to 60 months
Secondary: ADA incidence and characteristics and NAb	Section 13.1.7	Up to 60 months
Secondary: Rate of MRD[-] CR by investigator	Section 13.1.3.2.1	Up to 60 months
Secondary: Rate of MRD[-]	Section 13.1.3.2.1	Up to 60 months
Secondary: Duration of MRD negativity	Section 13.1.3.2.1	Up to 60 months
Phase 2a Dose Finding		
Primary: ORR	Section 13.1.3.1	Up to 60 months
Secondary: DOR by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: CBR by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: DCB by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: DCR (CBR + SD) by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: Duration of disease control by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: TTP by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: TTR by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: TTNT	Section 13.1.3.2.2	Up to 60 months
Secondary: PFS by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: OS	Section 13.1.3.2.2	Up to 60 months
Secondary: Frequency and severity of TEAEs	Section 13.1.8	Up to 60 months
Secondary: ADA incidence and characteristics and NAb	Section 13.1.7	Up to 60 months
Secondary: Rate of MRD[-] CR by investigator	Section 13.1.3.2.2	Up to 60 months
Secondary: Rate of MRD[-]	Section 13.1.3.2.2	Up to 60 months
Secondary: Duration of MRD negativity	Section 13.1.3.2.2	Up to 60 months

ADA: antidrug antibody; AE: adverse event; CBR: clinical benefit rate; CR: complete response; DCB: duration of clinical benefit; DCR: disease control rate; DLT: dose-limiting toxicity; DOR: duration of response; MRD: measurable (minimal) residual disease; MRD[-]: MRD negative; NAb: neutralizing antibody; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; SAE: serious adverse event; SD: stable disease; TEAE: treatment-emergent adverse event; TTNT: time to next treatment; TTP: time to progression; TTR: time to response.

6.3.4 Total Study Duration

The study is expected to enroll patients for approximately 12 to 18 months (phase 1 and phase 2a) and continue follow-up for a total study duration of approximately 60 months.

6.4 Randomization in Phase 2a Dose Finding

Patients will be randomized in a 1:1 ratio across 2 dose levels (DL1 or DL2) of modakafusp alfa in combination with daratumumab SC. Randomization will be stratified by the number of prior lines of therapy (1 vs 2 or 3).

Randomization procedures should be performed after complete eligibility assessments and before the initiation of assigned treatment. This study is unblinded.

6.5 Posttrial Access

At the end or termination of the study (Section 6.3.2), ongoing patients who continue benefiting from modakafusp alfa in combination with daratumumab SC, 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).

6.5.1 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, that patient's disease has progressed, or treatment is no longer tolerable).
- Either 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 posttrial protocol and informed consent.

6.5.2 Combination Agent

Only modakafusp alfa 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.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Patients aged 18 years or older.
2. Documented MM diagnosis per IMWG criteria.
3. Measurable disease, defined as at least 1 of the following:
   a. Serum M protein ≥0.5 g/dL (≥5 g/L) on serum protein electrophoresis (SPEP).
   b. Urine M protein ≥200 mg/24 hours on urine protein electrophoresis (UPEP).
   c. Serum free light chain (FLC) assay with involved FLC level ≥10 mg/dL (≥100 mg/L) provided serum FLC ratio is abnormal.
4. For patients in the phase 1 dose escalation only:
   Must have received at least 3 prior lines of 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) or therapy.
5. For patients in phase 2a dose finding only:
   a. Received 1 to 3 prior line(s) of antimyeloma therapy.
   b. Must be refractory to prior lenalidomide treatment.
   c. Patients must be sensitive (nonrefractory) or naïve to prior anti-CD38 mAb treatment.
   d. Documented progressive disease on or after the last regimen.
   e. Patients must have PR or better to at least 1 line of prior therapy.

   Note:

   A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3 to 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 on therapy or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease while on therapy.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at screening. (ECOG performance status scoring is provided in Appendix F.)

7. Adequate organ function at screening as determined by the following laboratory values:

Laboratory Test	Value
ANC [a]	≥1000/mm^3 (≥1.0 × 10^9/L)
Platelets [a]	≥75,000/mm^3 (≥75 × 10^9/L)
Hemoglobin	≥8.0 g/dL
Estimated creatinine clearance	≥30 mL/min (Cockcroft-Gault formula)
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 range.

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

8. The minimal interval between the last dose of any of the following treatments/procedures and the first dose of study drug must be at least:

Treatment/Procedure	Minimum Interval
Chemotherapy (including PIs), and IMiDs	14 days
Any investigational anticancer product	28 days or 5 half-lives whichever is longer
Antibody-based anticancer therapy	28 days or 5 half-lives whichever is longer
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	28 days

PI: proteosome inhibitor; IMiD: immunomodulatory drug.

9. Reproductively female patients who:
   - Are postmenopausal 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 (see Table 8.f) at the same time, from the time of signing the informed (e)consent form (ICF) through 3 months after the last dose of daratumumab SC, or 7 days after the last dose of modakafusp alfa, whichever is longer, OR

  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient during the entire study treatment period and through 3 months after the last dose of daratumumab SC, or 7 days after the last dose of modakafusp alfa, 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 an egg or eggs (ova) during the study and for 3 months after the last dose of daratumumab SC, or 7 days after the last dose of modakafusp alfa, whichever is longer.
  - Must also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

10. Reproductively male patients, unless surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception (see Table 8.f) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient during the entire study treatment period and through 7 days after the last dose of modakafusp alfa. (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 for 7 days after the last dose of modakafusp alfa.
    - Must also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.
11. Voluntary written or electronic consent (eConsent) must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

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

1. Prior exposure to modakafusp alfa.
2. Patient has POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, solitary plasmacytoma, amyloidosis, Waldenström macroglobulinemia, plasma cell leukemia, or lymphoplasmacytic lymphoma.
3. Patient has not recovered from adverse reactions to prior myeloma treatment or procedures (chemotherapy, immunotherapy, radiation therapy) to NCI CTCAE, Version 5 Grade ≤1 or baseline, except for alopecia.

4. Previous allogeneic stem cell transplant at any time or ASCT within 12 weeks of planned start of dosing.
5. 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 to have minimal risk of recurrence within 3 years.
6. Evidence of central nervous system involvement and/or meningeal involvement due to MM exhibited during screening.
7. 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/premedications, their analogues, or excipients in the various formulations of any agent per the prescribing information.
8. Patient is unable to take label-recommended/required prophylaxis needed for combination agents, ie, antiviral prophylaxis for daratumumab SC.
9. Seropositive for hepatitis B, or known history of seropositivity for hepatitis C or of seropositivity for HIV.
    - Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Patients with resolved infection (that is, patients who are HBsAg negative but positive for antibodies to hepatitis B core antigen and/or antibodies to HBsAg) 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: Participants with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody 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.
    - Seropositive for hepatitis C (anti-hepatitis C virus antibody positive or anti-hepatitis C virus–RNA quantitation positive), except in the setting of a sustained virologic response with undetectable hepatitis RNA level at least 12 weeks (negative viremia) after completion of antiviral therapy.
10. Patient has congestive heart failure (New York Heart Association Grade ≥II), cardiac myopathy, active ischemia, or any other uncontrolled cardiac condition such as angina pectoris, clinically significant arrhythmia requiring therapy including anticoagulants, or clinically significant uncontrolled hypertension.
11. Patient has a high risk of hemorrhage such as uncontrolled chronic bleeding disorder or is currently being treated with therapeutic anticoagulation.
12. Patient has a history of acute myocardial infarction within 5 months from enrollment or has electrocardiogram (ECG) abnormalities during screening that are deemed medically relevant by the investigator.

13. Patient has QT interval corrected by the Fridericia method >480 msec (Grade ≥2).
14. Patient has a concurrent illness that would preclude study conduct and assessment including but not limited to, uncontrolled medical conditions, uncontrolled and active infection (considered opportunistic, life threatening, or clinically significant), uncontrolled risk of bleeding, uncontrolled diabetes mellitus, pulmonary disease (including obstructive pulmonary disease, pulmonary fibrosis, and history of symptomatic bronchospasm), alcoholic liver disease, or primary biliary cirrhosis.
15. Patient has a chronic condition that will require the chronic use of systemic corticosteroids >10 mg/d of prednisone or equivalent on top of any required corticosteroids for MM.
16. Female patients who are lactating and breastfeeding or have 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 if applicable.
17. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

7.3 Excluded Prior Medications

Patients must not have received the final dose of any medications within the specified minimum intervals before first the dose of study drug as outlined in Section 7.1, Criterion 8.

Patients must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.4 Excluded Prior Procedures and Treatments

Patients must not have received the final dose of any of the procedures or treatments within the specified minimum intervals before the first dose of study drug as outlined in Section 7.1, Criterion 8.

8.0 STUDY DRUG

Investigational medicinal product: Modakafusp alfa.

Combination medicinal product: Daratumumab SC.

8.1 Study Drug Administration

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

8.1.1 Modakafusp Alfa

8.1.1.1 Dosage

Phase 1 dose escalation: 60, 80 (starting dose), 120, or 240 mg Q4W in 28-day cycles.

Phase 2a dose finding: 2 dose levels (DL1 and DL2) selected after the phase 1 dose escalation.

8.1.1.2 Administration

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

Daratumumab SC 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 daratumumab SC and the initiation of the infusion of modakafusp alfa.

If a patient presents with an IRR at any dose level, the duration of the infusion may be extended per the investigator's discretion. Infusion and pharmacy staff are advised to be prepared accordingly for either a planned, extended infusion time or for potential infusion interruptions. See the pharmacy manual for additional guidance.

8.1.1.3 Premedication

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 on by the sponsor.

The clinical site is responsible for sourcing all treatments administered before or after modakafusp alfa administration. In the event that a protocol-required medication for prophylactic coadministration is not able to be obtained by a clinical site due to regional drug availability, the medication may be supplied by the sponsor.

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

- Corticosteroid IV or orally (PO) (methylprednisolone 100 mg, dexamethasone 20 mg, or equivalent) 60 minutes to 2 hours before treatment. If a patient experiences no significant

IRR, the dose of methylprednisolone may be 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 mg to 1000 mg PO 60 minutes to 2 hours before treatment.
- Diphenhydramine or equivalent 25 mg to 50 mg PO approximately 12 hours before and again approximately 1 hour before Cycle 1 treatment; for all subsequent infusions, approximately 1 hour before.

Montelukast 10 mg PO may be given to patients who are intolerant to diphenhydramine or for whom diphenhydramine is ineffective.

On days on which the combination agent daratumumab and hyaluronidase-fihj is given on the same visit day as modakafusp alfa, administer the modakafusp alfa-specific premedication only (see Section 8.10.2).

8.1.1.4 Postinfusion Medication and Monitoring

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

During the infusion and for 2 hours after the end of infusion, the patient should be continually monitored by medically qualified staff with access to emergency medical equipment and medications to manage infusion reactions.

On days on which the combination agent daratumumab and hyaluronidase-fihj is given on the same visit day as modakafusp alfa, administer the modakafusp alfa-specific postinfusion medications only.

8.1.1.5 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.

8.1.2 Combination Agent Daratumumab SC

8.1.2.1 Dosage

Daratumumab SC: 1800 mg QW for Cycles 1 and 2, Q2W for Cycles 3 to 6, and Q4W thereafter in 28-day cycles.

8.1.2.2 Administration

Daratumumab SC will be administered SC 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 and the initiation of the infusion of modakafusp alfa.

8.1.2.3 Premedication

Before each injection, patients will receive the following premedication approximately 1 to 3 hours before the daratumumab and hyaluronidase-fihj on each dosing day (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022).

- 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.
- Antihistamine: 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 premedication only.

8.1.2.4 Postinjection Medication

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 from the day after the administration of daratumumab and hyaluronidase-fihj (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022).

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 in the event when corticosteroid is required as a premedication 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. After 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) 2022).

8.1.2.5 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 after EOT.

8.2 List of EU Auxiliary Medicinal Products

- Corticosteroids.
- Analgesics and antipyretics.
- Antihistamines.

- Leukotriene receptor antagonists.
- Antivirals.

8.3 DLT (Phase 1 Dose Escalation)

8.3.1 Definitions of DLT

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

Patients will be monitored through all cycles of therapy for toxicities. Primarily, only toxicities that occur during Cycle 1 will be used for the purposes of defining DLT.

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:

- Any Grade 5 AE.
- Hematologic toxicity, clearly unrelated to the underlying disease are defined as follows:
  - Nonfebrile Grade 4 neutropenia (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 single episode of body temperature >38.3°C (101°F) or sustained temperature 38.0°C (100.4°F) for more than 1 hour.
  - Grade 4 thrombocytopenia (platelets <25,000/mm^3) lasting more than 14 consecutive days.
  - Grade ≥3 thrombocytopenia (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 improve within 72 hours (reversion of Grade 4 events to Grade ≤2, reversion of Grade 3 events to Grade ≤1 or baseline).
  - Grade 3 nausea and/or emesis that can be controlled to Grade ≤2 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 within 7 days.
  - Grade 3 diarrhea that can be controlled to Grade ≤2 in ≤72 hours with appropriate treatment.
  - Grade 3 rash and pruritis that respond to standard treatment and resolve or improve to Grade ≤2 in ≤72 hours.
- Delay in the initiation of Cycle 2 by more than 14 days due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.

8.3.2 Definition of DLT-Evaluable Patients

The DLT-evaluable population will include patients in the dose escalation/de-escalation phase who either experienced a DLT in Cycle 1 in the treatment phase of the study, or who have completed the Cycle 1 dose of modakafusp alfa and received at least 75% of the planned dose of daratumumab SC.

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.

8.4 Dose Escalation Rules (Phase 1 Dose Escalation)

The rolling six design (Skolnik et al. 2008) will be implemented to guide the dose escalation/de-escalation to evaluate the safety and tolerability of modakafusp alfa in combination with daratumumab SC.

Rolling Six Design

In the rolling six design, up to 6 patients may be concurrently enrolled into a given dose level. Dose levels will be assigned, as outlined below, on the basis of the number of patients currently enrolled in the cohort, the number of DLTs observed, and the number of patients whose evaluation is pending at the time of new patient entry.

- Three to 6 patients may concurrently be enrolled in the study.
- Accrual to the study may be suspended if there are already 6 patients enrolled at the current dose level but not sufficient information to make the decision for the next action.
- Decisions as to whether to resume enrolling on the next dose level will be made using data available at the time of new patient enrollment.

- De-escalation will occur when 2 or more DLTs are observed at the current dose level regardless the number of patients enrolled. The current dose level will be considered toxic.
- If no more than 1 DLT is observed at the next higher dose level, escalation will occur when 3 of 3, 4 of 4, 5 of 5, 5 of 6, or 6 of 6 patients are enrolled at the current dose level with no DLT observed. If at least 2 DLTs have been observed at the next higher dose level, no escalation is allowed.
- In all other situations, patients will be enrolled and dosed at the current dose level up to a total of 6.

The initial dose level to be evaluated for modakafusp alfa will be 80 mg Q4W (Section 4.3). If 2 or more DLTs are observed at the starting dose level during the 28-day cycle, the dose for modakafusp alfa will be de-escalated to 60 mg Q4W. The modakafusp alfa 120 or 240 mg Q4W doses could be evaluated depending on the observed number of DLTs (observed in Cycle 1 of a 28-day cycle) as well as pending data as illustrated in Table 8.a. Daratumumab SC dosing will be administered according to the daratumumab SC (4-week cycle) prescribing information (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022). It is estimated that approximately 18 DLT-evaluable patients will be enrolled in the phase 1 dose escalation and at least 6 DLT-evaluable patients will be enrolled at the modakafusp alfa MTD in combination with daratumumab SC.

The dose escalation/de-escalation will stop when (1) the decision for the next patient is to be dosed at the next higher dose level and the next higher dose level is considered toxic (ie, ≥2 DLTs observed), or (2) the decision for the next patient is to be dosed at the next higher dose level and the current dose level is the highest dose level planned and 6 patients have already been evaluated, or (3) the decision for the next patient is to be dosed at the next lower dose level and 6 patients have already been evaluated with the next lower dose level, or (4) the decision for the next patient is to be dosed at the next lower dose level and the current dose level is the lowest dose level planned.

The MTD will be claimed as the highest dose level that has 6 evaluated patients with fewer than 2 DLTs.

Table 8.a Dose Escalation and De-escalation Rules

No. Patients Enrolled at Current Dose	No. DLTs	No. Without DLT	No. With Data Pending	If MTD Not Exceeded a	If MTD Exceeded b
2	0,1	Any	Any	Stay	Stay
2	2	0	0	De-escalate	De-escalate
3	0	0, 1, 2	3, 2, 1	Stay	Stay
3	0	3	0	Escalate	Stay
3	1	0, 1	2, 1	Stay	Stay
3	1	2	0	Stay	Stay

Table 8.a Dose Escalation and De-escalation Rules

No. Patients Enrolled at Current Dose	No. DLTs	No. Without DLT	No. With Data Pending	If MTD Not Exceeded a	If MTD Exceeded b
3	≥2	Any	Any	De-escalate	De-escalate
4	0	0, 1, 2	4, 3, 2	Stay	Stay
4	0	3	1	Stay	Stay
4	0	4	0	Escalate	Stay
4	1	0, 1	3, 2	Stay	Stay
4	1	2	1	Stay	Stay
4	1	3	1	Stay	Stay
4	≥2	Any	Any	De-escalate	De-escalate
5	0	0, 1, 2	5, 4, 3	Stay	Stay
5	0	3, 4	2, 1	Stay	Stay
5	0	5	0	Escalate	Stay
5	1	0, 1	4, 3	Stay	Stay
5	1	2	2	Stay	Stay
5	1	3, 4	1, 0	Stay	Stay
5	≥2	Any	Any	De-escalate	De-escalate
6	0	0, 1, 2	6, 5, 4	Suspend c	Suspend
6	0	3, 4	3, 2	Suspend	Suspend
6	0	5, 6	1, 0	Escalate	MTD
6	1	0, 1	5, 4	Suspend	Suspend
6	1	2	3	Suspend	Suspend
6	1	3, 4	2, 1	Suspend	Suspend
6	1	5	0	Escalate	MTD
6	≥2	Any	Any	De-escalate	De-escalate

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

a MTD not exceeded: no more than 1 DLT is observed at any dose level.

b MTD exceeded: 2 or more DLTs are observed at any dose level.

c "Suspend" means that enrollment will halt until sufficient DLT data is available to determine the action for the next new patient.

Additional patients are permissible to be enrolled if the stopping rule for dose escalation/de-escalation is not triggered after the last patient has been evaluated.

More conservative dose escalation, evaluation of intermediate doses or different dosing intervals, and expansion of an existing dose level are all permissible after discussions between the sponsor and the investigators if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or PD of modakafusp alfa in combination with daratumumab SC.

8.5 [redacted]

[redacted]

8.6 Dose Modification Guidelines

8.6.1 Modakafusp Alfa

8.6.1.1 Intrapatient Dose Escalation

No intrapatient dose escalation is planned for this study.

8.6.1.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

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

- ANC $\geq$1000/mm^3. Granulocyte-colony stimulating factor can be used to reach this level.
- Platelet count must be $\geq$50,000/mm^3. Platelet transfusion can be applied any time clinically indicated but should not be applied only for the purpose of meeting the treatment criterion of platelet count.

For therapy to resume, toxicity considered to be related to treatment with modakafusp alfa must have resolved to Grade $\leq$1 or baseline (Grade 2 for neutrophil and platelets), or to a level considered acceptable by the physician. If the above-cited criteria for retreatment are not met for a patient, 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.

8.6.1.3 Criteria for Dose Interruption

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to modakafusp alfa may continue study treatment with the same dose, may have modakafusp alfa treatment held, may have their dose reduced, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose, depending on the nature and severity of the AE and whether it is the first occurrence or is recurrent.

Table 8.b and Table 8.c provide general dose modification recommendations for nonhematologic and hematologic toxicities, respectively. Table 8.d 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 on discussion with the sponsor.

Table 8.b 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.d for the management of bleeding TEAEs and Table 8.g and Table 8.h 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 (see Table 8.e). 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.d or for the management of IRRs, which is found in Table 8.g, Table 8.h, and Section 8.10.1.1.

Table 8.c 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.d for the management of bleeding TEAEs and Table 8.g and Table 8.h 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 8.6.1.2 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.d or for the management of IRRs, which is found in Table 8.g, Table 8.h, and Section 8.10.1.1.

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

This table does not include guidance for management of IRRs. Refer to Table 8.g and Table 8.h 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.g, Table 8.h, and Section 8.10.1.1

8.6.1.4 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.e). 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.e 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	NA	60 mg

NA: not applicable.

8.6.1.5 Criteria for Discontinuation

In the dose escalation, 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. If treatment discontinuation is determined, the EOT visit should be completed within 30 days (+10 days) after the last administration of modakafusp alfa.

Patients who discontinue modakafusp alfa because of TEAEs assessed by the investigator as related *only* to modakafusp alfa may continue daratumumab SC treatment at the discretion of the investigator and with agreement by the sponsor.

8.6.2 Combination Drug

Dose modification, if any (dose change, interruption, discontinuation, etc.) of the combination drug (daratumumab SC) should be done in accordance with the 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 Prohibited Concomitant 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 progressive disease 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.
- 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, or if tumor flare is suspected.

- Live vaccines are not recommended.

8.8 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, granulocyte macrophage-colony stimulating factor) and erythropoietin are permitted. Their use should follow the product label, published guidelines, and institutional practice. Granulocyte colony stimulating factor is allowed to accelerate the recovery of neutropenia to enable the start of a new cycle (Section 8.6.1.2).
- 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 monoclonal antibodies like denosumab 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.
- Systemic steroids for acute management of pain, suspected or confirmed immune-mediated thrombocytopenia or other disease or treatment-related complications are permitted.
- Plasmapheresis.
- IV immunoglobulins 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.

8.9 Precautions and Restrictions

8.9.1 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 and should not donate sperm or ova. Patients of reproductive potential should use effective methods of contraception through defined periods during and after study treatment as specified below.

Reproductively female patients 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.f) at the same time, from the time of signing of the ICF through 3 months after the last dose of daratumumab SC, or 7 days after the last dose of modakafusp alfa, whichever is longer, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient during the entire study treatment period and through 3 months after the last dose of daratumumab SC, or 7 days after the last dose of modakafusp alfa, 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 an egg or eggs (ova) or breastfeed a baby during the study through 3 months after the last dose of daratumumab SC or 7 days after the last dose of modakafusp alfa, whichever is longer.
- Must also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

Reproductively male patients, unless surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception (see Table 8.f) during the entire study treatment period and through 7 days after the last dose of modakafusp alfa, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient during the entire study treatment period and through 7 days after the last dose of modakafusp alfa. (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 during the study and for 7 days after the last dose of modakafusp alfa

- Must also adhere to any applicable local (country-specified) treatment-specific pregnancy prevention guidelines.

Table 8.f Highly 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	

8.9.2 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, after authorization from the study participant's partner.

If a participant or a study participant's partner 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 up 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.

8.10 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed below, [redacted]

8.10.1 Modakafusp Alfa

8.10.1.1 IRRs

An IRR is a reaction that develops during or shortly after administration of a drug, and with modakafusp, an IRR can occur during any cycle. 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 8.1.1.3). Recommendations for premedications for the combination agent daratumumab SC are detailed in Section 8.1.2.3. On days on which the combination agent is administered 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. 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) 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.

If the patient continues on treatment, premedication and postinfusion medication should be considered for future modakafusp alfa administrations per Section 8.1.1.

All IRRs, including the signs and symptoms, will be reported in the eCRF per completion guidelines.

Serious AESIs will be reported to Takeda Global Pharmacovigilance in an expedited manner within 24 hours.

Grade 1 and 2 IRRs

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

Table 8.g 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 event of laryngeal edema, or Grade 2 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.h.

Table 8.h 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 event 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 of 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.

8.10.1.2 Low Platelet Count

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.d. The investigator can consider the usage of

corticosteroids, IV immunoglobulins 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.

8.10.1.3 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. Please also see Sections 8.1.1.5 and 8.1.2.5.

8.10.2 Combination Agent

Please refer to the product labels for daratumumab SC (Darzalex Faspro (daratumumab and hyaluronidase-fihj) 2022) 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.

8.11 Blinding and Unblinding

This is an open-label study.

8.12 Description of Investigational Agents

Modakafusp alfa and the combination agent daratumumab SC are described in Sections 4.1.2 and 4.1.3.1. Further details on modakafusp alfa may be found in the IB.

8.13 Preparation, Reconstitution, and Dispensation

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

Modakafusp alfa is an anticancer agent, and as with other potentially toxic compounds, caution should be exercised when handling modakafusp alfa.

Please refer to the pharmacy manual for the preparation of each dose of modakafusp alfa.

Please refer to the respective package insert for the preparation of daratumumab SC.

8.14 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.

Modakafusp alfa is supplied as sterile, lyophilized powder in a single-use, 20R stoppered glass vial with an aluminum flip-off seal, on reconstitution providing 10 mg/mL (50 mg) of modakafusp alfa.

Details for daratumumab SC and other comparator agents are provided in the respective package insert for each agent.

8.15 Storage, Handling, and Accountability

8.15.1 Modakafusp Alfa

Modakafusp alfa must be stored according to the manufacturer's stipulation in a dry place and at temperature as stated on the product labeling.

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 before the use of modakafusp alfa.

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 the 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) location 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.

If there is a discrepancy in product storage or handling between the protocol and other protocol related documentation, the product label shall supersede.

Further guidance and information are provided in the pharmacy manual.

8.15.2 Combination Agent

The combination agent (daratumumab SC) should be stored at temperatures in accordance with the instructions provided in the manufacturer's product label and information in the pharmacy manual. Additional details are provided in the respective package insert for each agent.

If there is a discrepancy in product storage or handling between the protocol and other protocol related documentation, the product label or commercial package (as applicable) shall supersede.

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 may be found in the study manual. A full list of investigators is available in Takeda's investigator database.

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

9.2 Arrangements for Recruitment of Patients

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

9.3 Informed (e)Consent

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

Patients consenting electronically (eConsent), where 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.

The requirements of informed consent are described in Section 15.2.

9.4 Treatment Group Assignments

During the phase 1 dose escalation, patients will be enrolled according to a rolling six design (see Section 8.4). During the phase 2a dose finding, patients will be randomized in a 1:1 ratio to treatment across 2 dose levels of modakafusp alfa in combination with daratumumab SC. Randomization will be stratified (see Section 6.1).

In phase 2a, the window allowed between randomization to Cycle 1 Day 1 dosing is 3 days.

9.5 Study Procedures

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

9.5.1 Patient Demographics

The date of birth or age, race, ethnicity, and sex of the patient are to be recorded during screening as permitted by local regulations.

9.5.2 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 the Revised International Staging System. Known cytogenetic alterations should be also collected. 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.

9.5.3 Physical Examination

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

If an investigator considers it safe and appropriate for a subject to miss a protocol-specified physical examination for coronavirus disease 2019 (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.

9.5.4 Patient Height and Weight

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

9.5.5 Vital Signs

Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. They include also supine or seated measurements of diastolic and systolic blood pressure (after 3 to 5 minutes in this position; all measurements should be performed in the same initial position). They will be measured at the times specified in in the SOEs (Appendix A). Vital signs will be measured at any time a patient complains of symptoms consistent with IRR or clinically indicated. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient cannot be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour. Patients must be observed for at least 2 hours after the end of the infusion of modakafusp alfa in each cycle when modakafusp is administered.

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 10.2.

9.5.6 Pregnancy Test

Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug. A urine or serum pregnancy test will be required during screening and at baseline (within 72 hours before the start of study drug). A participant of childbearing potential is defined as a reproductive female who (1) has not undergone a hysterectomy or bilateral oophorectomy or (2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

During the study, 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 before dosing. Pregnancy tests may also be repeated during the study per request of the IRB or if required by local regulations.

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

9.5.7 Concomitant Medications and Procedures

Any prior or concomitant medication a patient has had from signing of the ICF through 30 (+10) days after the last dose of study drug treatment (modakafusp alfa and/or daratumumab SC) or the start of subsequent systemic anticancer therapy, whichever occurs first, will be recorded on the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication will be recorded. Medications used by the patient and therapeutic procedures (including any transfusion) completed by the patient will be recorded in the eCRF. See Sections 8.7 and 8.8 regarding medications and therapies that are prohibited or allowed, respectively, during the study.

9.5.8 ECOG Performance Status

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

9.5.9 AEs

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

9.5.10 Enrollment

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

Rescreening is permitted if deemed appropriate by the investigator upon consultation with the sponsor when a patient might meet all the eligibility criteria with the cause(s) of previous screening failure being resolved.

9.5.11 ECG

A 12-lead ECG will be obtained 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.

9.5.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally.

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

9.5.12.1 Clinical Chemistry, Hematology, Urinalysis and Indirect Antiglobulin Test (Coombs Test)

Blood samples will be obtained for analysis of clinical chemistry, hematology, and urinalysis as shown in Table 9.a, Table 9.b, and Table 9.c, respectively. Samples will be obtained at time points as specified in the SOEs (Appendix A).

Table 9.a Clinical Chemistry

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

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

Estimated creatinine clearance

$$= [(140\text{-Age}) * \text{weight(kg)}] / [72 * \text{serum creatinine(mg/dL)}]$$

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

Table 9.b Hematology Tests

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

ANC: absolute neutrophil count.
[a] Differential to include basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

Table 9.c Urinalysis

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 clinical laboratory tests are outlined in Table 9.d.

Table 9.d Other Laboratory Tests

Serum β_2 microglobulin	Blood type, Rh factor and indirect antiglobulin test (indirect Coombs test)
Thyroid function test (TSH, T4, T3)	Hepatitis B serology
HBV DNA test	

HBV: hepatitis B virus; Rh: Rhesus; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone/thyrotropin.

9.5.13 Disease Assessment

Unless otherwise specified as detailed in the SOEs (Appendix A), response assessment for phase 1 dose escalation and phase 2a dose finding will be made locally. Disease assessment will be conducted per the SOEs (Appendix A) and evaluated according to IMWG criteria (Appendix E).

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.

Serum and urine response assessments will be performed as indicated in the SOE (Appendix A).

Imaging tests for qualifying patients are to be performed every 12 weeks beginning with Cycle 3 only for patients with extramedullary disease at screening or when there is a clinical suspicion of extramedullary progression. Investigators will assess disease response/status. Response and relapse categories are described in Appendix E.

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 (locally) is required to document a CR; no second bone marrow confirmation is needed. At the time of collecting BMA samples to confirm CR locally, a BMA sample will be also collected for central analysis of MRD as the first pull.

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.

The disease assessments outlined in the following sections will be performed as shown in the SOEs (Appendix A).

9.5.13.1 Extramedullary Disease Imaging

Imaging will be evaluated locally for all patients. For patients with previously documented extramedullary disease or with suspicion of extramedullary progression, a positron emission tomography-computed tomography (PET-CT) scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, they 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 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 progressive disease.

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

9.5.13.2 Bone Imaging

Imaging will be evaluated locally for all patients. Whole body bone imaging will be performed at screening (if the patient has adequate image test performed within 5 weeks of the planned first dose of study drug, they 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 total body CT scan or whole body MRI or PET-CT (Hillengass et al. 2019). A conventional skeletal survey should only be done if other imaging modalities are not available. If there are symptoms or signs that suggest increased or new bone lesions, either whole body bone imaging or localized imaging of symptomatic sites may be repeated any time during the study and at the EOT visit. The same modality for assessment 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.

Radiographs will be analyzed locally and reports maintained with the patient record for retrieval during monitoring visits.

9.5.13.3 Quantification of Immunoglobulins

A blood sample for quantification of immunoglobulins (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 immunoglobulins (in addition to quantitative IgM, IgG, and IgA). Analysis of immunoglobulins will be performed locally.

9.5.13.4 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).

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

9.5.13.5 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.

9.5.13.6 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 testing will be performed locally.

9.5.13.7 Interference Assay

IgG mAbs given recently as prior therapy can interfere with assays used to monitor endogenous M-protein. The SPEP and serum immunofixation can be positive due to mAb. This interference can impact the determination of CR and of disease progression in some patients with IgG myeloma protein. Therefore, in patients with persistent VGPR by IMWG criteria where mAb interference is suspected or whenever the SPEP values reach ≤0.2 g/dL for 2 consecutive disease evaluations during a period of time when the mAb could be circulating at detectable levels, a CR should be suspected triggering the need for interference testing on the M-protein sample at the central laboratory. Currently, if the interference test results are positive, the assay is considered positive for endogenous protein, and thus there is still disease present. If the interference test result is negative, the assay is considered negative for endogenous protein, and thus the remaining protein is likely the mAb. This is communicated back to the sites, and the sites can proceed to perform a confirmatory BMA evaluation for possible CR if not already performed earlier.

9.5.13.8 Bone Marrow Aspirate

Bone marrow samples will be collected as specified in Appendix A.

9.5.13.9 Local Laboratory Evaluations

9.5.13.9.1 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 progressive disease 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 E).

9.5.13.9.2 Cytogenetics

The most recent cytogenetic results from samples taken between diagnosis and before study enrollment will be requested as part of medical history of the patients. The historical cytogenetic evaluation should have been analyzed locally, according to local standards, if the site has the capability to perform analysis using methodologies such as fluorescence in situ hybridization and/or conventional cytogenetics (karyotype).

All patients should also have a sample from screening sent for central analysis (BMA for cytogenetics).

9.5.13.10 Central Laboratory Evaluations

BMA for MRD

For all patients, a BMA for MRD sample to determine rate and duration of MRD negativity should be collected at screening at the same time as the BMA and biopsy procedure is performed for local disease assessment purposes. Additionally, when a CR is suspected based on laboratory values, per routine clinical practice (Appendix E), a BMA should be drawn for local disease assessment and central analysis of MRD. Additionally for patients with a confirmed CR, BMAs for MRD should be collected at 6, 12, and 24 months following CR confirmation. 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. These evaluations will be performed at a central laboratory.

BMA for Cytogenetics

During the screening period, an additional 3 mL pull of bone marrow (fresh BMA) will be collected, on completion of the BMA for MRD sample collection, to centrally analyze a broad spectrum of cytogenetic abnormalities and [redacted], perform immunoprofiling, [redacted], and plasma biomarker evaluation. Where country guidelines and/or regulations prohibit genomic analysis, a fluorescent in-situ hybridization will be used to evaluate

cytogenetic abnormalities and remaining biomarker assessments limited to immunoprofiling and plasma analysis.

[redacted]

9.5.14 Biomarker, PD, and PK Samples

9.5.14.1 Primary Specimen Collection

Table 9.e summarizes primary specimen collection for the study.

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 (Appendix B) and biomarker assessments. Bone marrow biopsy and aspirate collections are specified in the SOE (Appendix A).

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

Table 9.e Primary Specimen Collection

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Serum sample for modakafusp alfa PK	Blood	Serum	Modakafusp alfa concentrations	Mandatory [a]
Serum sample for daratumumab PK	Blood	Serum	Daratumumab concentrations	Mandatory [a]
BMA for MRD	BMA	DNA	Biomarker measurements	Mandatory [a]
BMA for cytogenetics	BMA	DNA, RNA, plasma and immune cells	Biomarker measurements	Mandatory [a]
[redacted]				
Serum sample for immunogenicity	Blood	Serum	Immunogenicity measurement (ADA and NAb)	Mandatory
Blood sample for flow cytometry	Blood	N/A	Biomarker measurements	Mandatory
Serum sample for circulating biomarkers	Blood	Serum	Biomarker measurements	Mandatory
Blood sample for RNA	Blood	RNA	Biomarker measurements	Mandatory [a]
[redacted]				

ADA: antidrug antibody; BMA: bone marrow aspirate; MRD: measurable (minimal) residual disease; NAb: neutralizing antibody; PK: pharmacokinetics.

[a] Mandatory unless local regulations prohibit.

9.5.14.2 PK Sampling

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 B.

The timing, but not the total number of samples, may be modified during the study on the basis of emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK of modakafusp alfa and/or daratumumab.

9.5.14.3 [redacted]

9.5.14.3.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.5.14.3.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.5.15 [redacted]

[redacted]

[redacted]

[redacted]

9.5.16 Immunogenicity Sample Collection

Serum samples prepared from blood for assessment of immunogenicity will be collected at time points specified in the SOE (Appendix A) and as outlined in the laboratory manual. Samples must be collected before either 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 8.10.1.1). Samples confirmed ADA positive against modakafusp alfa will be assayed for the ADA titer and domain specificity characterization as well as their neutralizing ability. If serum PK samples from the modakafusp alfa in combination with daratumumab SC indicate a loss of detectible daratumumab PK, ADA against daratumumab may be evaluated as sample volume supports. [redacted]. These samples will be analyzed at a central laboratory (Appendix A).

9.6 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 9.8. 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.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they withdrew from the study for any reason outlined in Section 9.9.

9.8 Discontinuation of Treatment With Study Drug and Patient Replacement

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

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

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

- AE.
- Protocol deviation.
- Progressive disease.
- Symptomatic deterioration.
- Confirmed pregnancy.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

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

In the case of study termination by the sponsor, eligible patients may have continued access to modakafusp alfa as described in Section 6.5.

Only patients who are withdrawn from treatment during Cycle 1 during the safety lead-in for reasons other than DLT will be replaced.

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

9.9 Withdrawal of Patients From Study

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

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

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

9.10 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.

9.11 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than progressive disease will continue to have PFS visits. The PFS visits should occur every 4 weeks from the EOT until the occurrence of progression, death, the start of subsequent systemic antineoplastic therapy, study termination, whichever occurs first. OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal. Imaging tests for patients with extramedullary disease should be performed every 12 weeks or if new symptoms suggest progressive disease.

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 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient who has provided informed (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 AESI

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 Takeda are provided in Section 10.2.

10.1.4 SAE Definition

SAE means any untoward medical occurrence that at any dose:

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

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

In this study, intensity for each AE, including any laboratory 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_Reference_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 Recording and Reporting AEs and SAEs

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

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

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an

EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

Planned hospital admissions or surgical procedures for an illness or disease that existed before 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 study manual.

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

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of informed (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).

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 study manual.

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 study manual.

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

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

Completed eCRFs are required for each patient who signs an informed (e)consent.

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed (e)consent forms, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of

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

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

The investigator and the head of the institution are required to retain essential relevant documents until the later of:

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification that investigation was discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

Should the sponsor request a longer retention period, the head of the institution should discuss how long and how to retain those documents with the sponsor. In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

When proceeding to a local post-marketing study, the investigator and the head of the institution are required to retain essential relevant documents until the later of the end of the re-examination or re-evaluation. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

In general, summary tabulations will be presented by dose level for the phase 1 dose escalation and phase 2a dose finding, and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous data, and the number and percentage per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25th, 50th (median), and 75th percentiles (if estimable) will be provided along with their 95% CIs for time-to-event data.

Deviations from the statistical analyses outlined in this protocol will be indicated in the statistical analysis plan; any further modifications will be noted in the final clinical study report.

13.1.1 Analysis Sets

The populations used for analyses will include the following:

- **DLT-evaluable population**: The DLT-evaluable population will include patients from the phase 1 dose escalation who experienced a DLT in Cycle 1 in the treatment phase of the study or have completed the Cycle 1 dose of modakafusp alfa and at least 75% of the planned dose of daratumumab SC. The DLT-evaluable population will be used to inform the 2 dose levels for modakafusp alfa to be selected in the phase 2a dose finding in combination with daratumumab SC.
- **Safety population**: The safety population is defined as all patients (phase 1 dose escalation and phase 2a dose finding) who receive at least 1 dose, even an incomplete dose, of any study drug. Patients will be analyzed according to the actual treatment they received for the safety population.
- **Intent-to-treat (ITT) population**: The ITT population is defined as all patients in the phase 2a dose finding who are randomized. Patients in this population will be analyzed according to the treatment they were randomized to receive, regardless of any dosing errors.
- **Per protocol population**: The per protocol population is a subset of the safety population that includes subjects who do not have major protocol deviations that are considered to have an effect on efficacy outcomes. The list of major protocol deviations is maintained by the sponsor on an ongoing basis and will be finalized before the primary analysis of the study.
- **Response-evaluable population**: The response-evaluable population is defined as patients who receive at least 1 dose, even an incomplete dose, of any study drug, have a disease assessment at screening (baseline evaluation), and at least 1 postbaseline disease assessment.
- **PK-evaluable population**: The PK-evaluable population includes patients from the safety population with sufficient PK data to reliably report 1 or more PK parameters.
- **Immunogenicity-evaluable population**: The immunogenicity-evaluable population includes patients who received at least 1 dose of modakafusp alfa in combination with daratumumab

SC (partial or complete) with a baseline assessment and at least 1 postbaseline immunogenicity assessment.

13.1.2 Analysis of Demographics 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, 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. No inferential statistics will be carried out.

13.1.3 Efficacy Analysis

All available efficacy data will be included in data tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified.

Disease responses are assessed by the investigator per IMWG criteria, unless otherwise stated.

13.1.3.1 Analysis of Primary Efficacy Endpoint

ORR

ORR is defined as the proportion of patients who achieved a confirmed PR or better during the study. The analysis will be based on the safety population for the phase 2a dose finding with responses assessed by the investigator per IMWG criteria. ORR proportions and associated 2-sided 95% exact binomial CIs will be presented for each treatment arm. No formal statistical test will be performed to compare the 2 treatment arms.

Sensitivity analyses for ORR include, but not limited to:

1. ORR assessed by investigator will be analyzed using the ITT population.
2. ORR assessed by investigator will be analyzed using the per protocol population.

13.1.3.2 Analysis of Secondary Efficacy Endpoints

13.1.3.2.1 Phase 1 Dose Escalation

For the phase 1 dose escalation, secondary efficacy endpoints include ORR, DOR, PFS, OS, MRD[-] CR rate, MRD[-] rate, and duration of MRD negativity.

All disease responses are assessed by the investigator per IMWG criteria.

ORR, MRD[-] CR Rate and MRD[-] Rate

ORR is defined in Section 13.1.3.1. The analysis will be based on the response-evaluable population.

MRD[-] CR rate is defined as the proportion of patients who have achieved confirmed CR assessed by the investigator and MRD[-] status using a threshold of 10^{-5}. The analysis will be based on the response-evaluable population.

MRD[-] rate is defined as the proportion of patients who have achieved MRD[-] status using a threshold of 10^{-5}. The analysis will be based on the response-evaluable population.

All these endpoints will be summarized by mean proportions and 2-sided 95% exact binomial CIs for each dose level.

DOR, PFS, OS, and Duration of MRD Negativity

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

PFS is defined as the time from the date of the first dose administration of any study drug to the first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. Patients without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment. The analysis will be based on the safety population.

OS is defined as the time from the date of the first dose administration of any study drug to the documentation 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. The analysis will be based on the safety population.

Duration of MRD negativity for patients achieving MRD negativity is defined as the time from the date of first documentation of MRD negativity to the first documentation of MRD positivity or confirmed progressive disease, whichever occurs first. It will be calculated for patients achieving MRD negativity only. Patients without documentation of MRD positivity or confirmed progressive disease will be censored at the date last known to be MRD negativity.

For these endpoints, K-M survival curves and K-M medians (if estimable), together with 95% CIs, may be calculated if appropriate.

13.1.3.2.2 Phase 2a Dose Finding

Secondary efficacy endpoints include DOR, CBR, DCB, DCR, duration of disease control, TTP, TTR, TTNT, PFS, OS, MRD[-] CR rate, MRD[-] rate, and duration of MRD negativity for patients achieving MRD negativity.

All disease responses are assessed by the investigator per IMWG criteria.

CBR, DCR, MRD[-] CR Rate, and MRD[-] Rate

CBR is defined as the proportion of patients who had a confirmed response of sCR, CR, VGPR, PR, or minimal response based on investigators' disease assessment per IMWG criteria.

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

MRD[-] CR rate is defined in Section 13.1.3.2.1.

MRD[-] rate is defined in Section 13.1.3.2.1.

CBR, DCR, MRD[-] CR rate, and MRD[-] rate as well as associated 95% exact binomial CIs will be presented for each treatment arm. These analyses will be based on the safety population.

DOR, DCB, Duration of Disease Control, TTP, TTNT, PFS, OS, and Duration of MRD Negativity for Patients Achieving MRD Negativity

DOR and duration of MRD negativity are defined in Section 13.1.3.2.1.

DCB is defined as the time from the date of first documentation of a minimal response or better to the date of first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. DCB will be calculated for only patients who achieved a minimal response or better. Patients without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment.

Duration of disease control is defined as the time from date of first documentation of SD or better to the date of first documentation of confirmed progressive disease or death due to any cause. Duration of disease control will be calculated for only patients who achieved SD or better. Patients without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment.

TTP is defined as the time from the date of randomization to the first documentation of confirmed progressive disease as defined by IMWG criteria. Patients without documentation of confirmed progression will be censored at the date of last adequate disease assessment. The analysis will be based on the ITT population.

TTNT is defined as the time from the date of first dose administration of any study drug to the date of the first dose initiation of the next line of anticancer therapy for any reason or death from any cause, whichever comes first. Patients who have not started the next-line therapy will be censored at the date last known to be alive before subsequent anticancer therapy. The analysis will be based on the safety population.

PFS is defined as the time from the date of randomization to the first documentation of confirmed progressive disease or death due to any cause, whichever occurs first. Patients without documentation of confirmed progressive disease or death will be censored at the date of last adequate disease assessment. The analysis will be based on the ITT population.

OS is defined as the time from the date of randomization to the documentation 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. The analysis will be based on the ITT population.

Disease responses are assessed by the investigator per IMWG criteria. K-M survival curves and K-M medians (if estimable), together with 95% CIs, will be calculated for each arm.

TTR

TTR is defined as time from the date of first dose administration of any study drug to the date of the first documentation of a confirmed PR or better. TTR will be calculated for responders only and summarized as a continuous variable. Mean TTR as well as associated 95% CI for each arm will be presented.

13.1.4 PK Analysis

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

13.1.5 [redacted]

[redacted]

13.1.6 PK/PD Analysis

The PK and PD data collected in this study may contribute in future population PK/PD analyses conducted to characterize the E-R relationships between modakafusp alfa and daratumumab serum exposure and response (eg, serum M-protein, platelet count). These population PK/PD analyses may include data collected in other modakafusp alfa clinical single or combination studies. The analysis plan for the PK/PD analysis will be separately defined, and the results of these analyses, if conducted, will be reported separately.

13.1.7 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]

[redacted]

13.1.8 Safety Analysis

AEs will be summarized using the safety population.

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

Exposure to study drug over time will be summarized with time on treatment, total amount of administered treatment, dose intensity, and relative dose intensity. Reasons for treatment discontinuation and modification 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 or start of subsequent anticancer therapy, whichever occurs first will be tabulated. All AEs will be coded using the Medical Dictionary for Regulatory Activities. Data will be summarized using Preferred Term and/or primary System Organ Class and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- Grade 5 TEAEs.
- Grade 5 drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients).
- SAEs (related and regardless of relationship).
- SAEs Grade 3 or higher.
- Drug-related SAEs Grade 3 or higher.
- AESIs Grade 3 or higher.
- TEAE leading to study drug modification and discontinuation.

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

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.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs, weight and ECOG performance status scores will be tabulated by scheduled time points.

Physical examination findings will be presented in the data listings.

13.2 Determination of Sample Size

A total of approximately 58 patients will be enrolled in the study, including approximately 18 DLT-evaluable patients for the phase 1 dose escalation and approximately 40 patients (approximately 20 patients per arm) for the phase 2a dose finding.

The phase 1 dose escalation will accrue approximately 18 DLT-evaluable patients based on the algorithm of the rolling six design.

With approximately 20 patients per arm in the phase 2a dose finding, the probability of observing at least 1 AE given a different true AE rate is as follows:

True AE rate	5%	10%	15%	20%
Probability of observing at least 1 AE	64%	88%	96%	99%

With approximately 20 patients per arm in the phase 2a dose finding, the 95% exact binomial CIs associated with different observed ORR are as follows:

Observed ORR	60%	70%	80%
95% CI	(0.361, 0.809)	(0.457, 0.881)	(0.563, 0.943)
Width of the 95% CI	0.448	0.424	0.379

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. Where permitted by local and country regulations, alternative approaches such as remote source data review via phone or video may be used to ensure data quality and integrity and patient safety. Additional details are in the monitoring plan. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

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

14.2 Protocol Deviations

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

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

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a 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 US Food and Drug Administration [FDA], the

United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (herein "patients") according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix C. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

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

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

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment

materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

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

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

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

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

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

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

time of (e)consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

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

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

15.3 Patient Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public

disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

Data Sharing

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

Abecma (idecabtagene vicleucel) suspension for intravenous infusion 2021. Prescribing Information. Summit, NJ: Celgene Corporation.

Blenrep (belantamab mafodotin-blmf) 2020. Prescribing Information. Brentford, UK: GlaxoSmithKline.

Carvykti (ciltacabtagene autoleucel) Suspension for Intravenous Infusion 2022. Full Prescribing Information. Horsham, PA: Janssen Biotech, Inc.

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.

Collins, S., Joshi, A., Shen, L., Das, S., Suryanarayan, K., Bottino, D., et al. 2020. TAK-573, an anti-CD38–attenuated interferon alpha (IFNα) fusion protein (Attenukine™), has demonstrated IFNα receptor (IFNAR) pathway modulation in patients with relapsed/refractory multiple myeloma. Abstract No. 357. *J Immunother Cancer,* 8(Suppl 3), A218.

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 Faspro (daratumumab and hyaluronidase-fihj) 2022. Full Prescribing Information. Horsham, PA: Janssen Biotech, Inc.

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.

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.

Mateos, M. V., Nahi, H., Legiec, W., Grosicki, S., Vorobyev, V., Spicka, I., et al. 2020. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol,* 7(5), e370-e80.

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. *American Journal of Clinical Oncology,* 5(6), 649-55.

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.

Richard, S., Jagannath, S., Cho, H. J., Parekh, S., Madduri, D., Richter, J., et al. 2021. A comprehensive overview of daratumumab and carfilzomib and the recently approved daratumumab, carfilzomib and dexamethasone regimen in relapsed/refractory multiple myeloma. *Expert Rev Hematol,* 14(1), 31-45.

Sarclisa (Isatuximab) 2020. Package Insert. Bridgewater, NJ: Sanofi-Aventis.

Skolnik, J. M., Barrett, J. S., Jayaraman, B., Patel, D. and Adamson, P. C. 2008. Shortening the timeline of pediatric phase I trials: the rolling six design. *Journal of Clinical Oncology,* 26(2), 190-5.

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.

Appendix A Schedules of Events

Table 1 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Screening**	**Cycle 1 (28 d/cycle)**					**Cycle 2 (28 d/cycle)**				
Day		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**
Window Allowed	**≤21 d**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±3d**	**0**	**±3 d**	**±3 d**	**±3 d**
Informed consent [a]	X										
Eligibility criteria	X										
Demographics	X										
Medical history	X										
Prior medication and treatment history	X										
Height and weight [b]	X	X					X				
ECOG performance status	X	X					X				
12-lead ECG [c]	X	X					X				
Physical examination (may be symptom-directed after screening visit)	X	X		X	X	X	X		X	X	X
Vital signs [d]	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 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 start of subsequent anticancer therapy, whichever occurs first (see Section 10.3)										
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (see Section 10.3)										
Dosing											
Modakafusp alfa infusion [f]		X					X				
Daratumumab SC		X		X	X	X	X		X	X	X
Safety Laboratory Assessments											
Chemistry [i] *(local)*	X	(X)		X	X	X	X		X	X	X
Hematology [j] *(local)*	X	(X)		X	X	X	X		X	X	X

Table 1 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Screening**	**Cycle 1 (28 d/cycle)**					**Cycle 2 (28 d/cycle)**				
Day		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**
Window Allowed	**≤21 d**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±3d**	**0**	**±3 d**	**±3 d**	**±3 d**
Thyroid function tests *(local)* [w]	X										
Urinalysis *(local)* [k]	X										
Pregnancy test *(local)* [l]	X	X					X				
Hepatitis B serology *(local)*	X										
HBV DNA *(local)* [kk]	X										
Serum β_2 microglobulin *(local)*	X										
Blood type, Rh factor, and indirect Coombs test *(local)* [gg]	X										
Disease Assessments											
Serum M-protein *(local)* [m]	X	(X) [m]					X				
24-hour urine M-protein *(local)* [o]	X	(X) [o]					X				
Serum FLC assay *(local)* [p]	X	(X) [p]					X				
Immunofixation: serum and urine *(local)* [q]	X	(X) [q]					X				
Quantification of immunoglobulins *(local)* [r]	X	(X) [r]					X				
Serum sample for interference testing (*central*) [ii]							(X)				
BMA for disease assessment *(local)* [s]	X	Sample to be collected at suspected CR to confirm response (CR/sCR)									
BMA for cytogenetics (*central*) [ee, hh]	X [u]										
BMA for MRD *(central)* [dd]	X	Sample to be collected at suspected CR and additional time points per description in footnote [dd]									
Investigator assessment of disease response/status							X				
Imaging Assessments											
Bone imaging [g]	X	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or progressive disease)									
Extramedullary disease imaging [h]	X	Additional assessments for extramedullary disease per the imaging schedule (Section 9.5.13.1)									

Table 1 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Screening**	**Cycle 1 (28 d/cycle)**					**Cycle 2 (28 d/cycle)**				
Day		**D1**	**D2**	**D8**	**D15**	**D22**	**D1**	**D2**	**D8**	**D15**	**D22**
Window Allowed	**≤21 d**	**0**	**0**	**±2 d**	**±2 d**	**±2 d**	**±3d**	**0**	**±3 d**	**±3 d**	**±3 d**
Clinical assessment of imaging response/status [e, g, h]		Additional assessments to be done per the imaging schedule Section 9.5.13.1 and 9.5.13.2									
Biologic Laboratory Assessments *(central analysis)*											
Serum sample for PK [t]		Refer to PK collection Appendix B, Table 1									
Serum sample for immunogenicity (ADA/NAb) [x, hh]		X			X		X			X	
Blood sample for flow cytometry [v]		X [cc]	X [n]	X	X	X	X [cc]	X [n]	X	X	X
Serum sample for circulating biomarkers [v]		X [cc]	X [n]	X	X	X	X [cc]	X [n]	X	X	X
Blood sample for RNA [v, ff]		X [cc]	X [n]	X	X	X	X [cc]	X [n]	X		
[redacted]											

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMA: bone marrow aspirate; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D: day; Dara: daratumumab SC; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; HBV: hepatitis B virus; HCO_3^-: bicarbonate; ICF: informed consent form; IRR: infusion-related reaction; LDH: lactate dehydrogenase; Moda: modakafusp alfa; MRD: measurable (minimal) residual disease; MRI: magnetic resonance imaging; NAb: neutralizing antibody; OS: overall survival; PET-CT: positron emission tomography-computed tomography; PCR: polymerase chain reaction; PFS: progression-free survival; PK: pharmacokinetic(s); RBC: red blood cell; Rh factor: Rhesus factor; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; WBC: white blood cell.

Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

Footnotes for Schedule of Events (SOE) Tables 1 and 2 appear after SOE Table 2.

Table 2 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Cycle 3 (28 d/cycle)**		**Cycle 4 (28 d/cycle)**		**Cycle 5 (28 d/cycle)**			**Cycle 6 (28 d/cycle)**		**Cycle 7 and beyond (28 d/cycle)**	**Cycle 11 (28 d/cycle)**		**EOT** 30 (+10) d after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [z]	**FU**	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D2**	**D15**	**D1**	**D15**	**D1**	**D1**	**D2**		**PFS** Q4W (±1 wk) [aa]	**OS** Q12W (±1 wk) [bb]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**0**			
Weight	X		X		X			X		X	X				
ECOG performance status	X		X		X			X		X	X		X		
12-lead ECG [c]	X		X		X			X		X	X		X		
Physical examination (may be symptom-directed)	X	X	X	X	X		X	X	X	X	X		X		
Vital signs [d]	X	X	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 (see Section 10.3)														
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (see Section 10.3)														
Dosing															
Modakafusp alfa infusion [f]	X		X		X			X		X	X				
Daratumumab SC	X	X	X	X	X		X	X	X	X	X				
Safety Laboratory Assessments															
Chemistry *(local)* [i]	X		X		X			X		X	X		X		
Hematology *(local)* [j]	X	X	X	X	X		X	X	X	X	X		X		
Pregnancy test *(local)* [l]	X		X		X			X		X	X		X		
Thyroid function tests *(local)* [w]	X							X		X [w]			X		
HBV-DNA *(local)* [kk]	Every 12 weeks (± 1 week) from Cycle 1 Day 1 until 6 months after the last dose of daratumumab SC														

Table 2 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Cycle 3 (28 d/cycle)**		**Cycle 4 (28 d/cycle)**		**Cycle 5 (28 d/cycle)**			**Cycle 6 (28 d/cycle)**		**Cycle 7 and beyond (28 d/cycle)**	**Cycle 11 (28 d/cycle)**		**EOT** 30 (+10) d after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [z]	**FU**	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D2**	**D15**	**D1**	**D15**	**D1**	**D1**	**D2**		**PFS** Q4W (±1 wk) [aa]	**OS** Q12W (±1 wk) [bb]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**0**			
Disease Assessments															
Serum M-protein [m] *(local)*	X		X		X			X		X	X		(X) [y]	X	
24-hour urine M-protein *(local)* [o]	X		X		X			X		X	X		(X) [y]	X	
Serum FLC assay *(local)* [p]	X		X		X			X		X	X		(X) [y]	X	
Immunofixation: serum and urine [q] *(local)*	X		X		X			X		X	X		(X) [y]	X	
Serum sample for interference testing *(central)* [ii]	(X)		(X)		(X)			(X)		(X)	(X)		(X) [y]	(X)	
Quantification of immunoglobulins *(local)* [r]	X		X		X			X		X	X		(X) [y]	X	
BMA for disease assessment *(local)*	Sample to be collected at suspected CR to confirm response (CR/sCR); optional at the time of progression														
BMA for MRD *(central)* [dd]	Sample to be collected at suspected CR and additional time points per description in footnote [dd]														
[redacted]															
Investigator assessment of disease/response status	X		X		X			X		X	X		X	X	
Imaging Assessments															
Bone imaging [g]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or progressive disease)														
Extramedullary disease imaging [h]	Additional assessments for extramedullary disease per the imaging schedule (Section 9.5.13.1)														
Clinical assessment of imaging	Additional assessments to be done per the imaging schedule Sections 9.5.13.1 and 9.5.13.2														

Table 2 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation

Study Period/Cycle	**Cycle 3 (28 d/cycle)**		**Cycle 4 (28 d/cycle)**		**Cycle 5 (28 d/cycle)**			**Cycle 6 (28 d/cycle)**		**Cycle 7 and beyond (28 d/cycle)**	**Cycle 11 (28 d/cycle)**		**EOT** 30 (+10) d after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [z]	**FU**	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D2**	**D15**	**D1**	**D15**	**D1**	**D1**	**D2**		**PFS** Q4W (±1 wk) [aa]	**OS** Q12W (±1 wk) [bb]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**0**			
response/status [e, g, h]															
Biologic Laboratory Assessments (central analysis)															
Serum sample for PK [t]	Refer to PK collection Appendix B, Table 2														
Serum sample for immunogenicity (ADA/NAb) [x, hh]	X		X		X			X		X	X		X	X	
Blood sample for flow cytometry [v]					X [cc]	X [n]					X [cc]	X [n]	X		
Serum sample for circulating biomarkers [v]					X [cc]	X [n]					X [cc]	X [n]	X		
Blood sample for RNA [v, ff]					X [cc]	X [n]					X [cc]	X [n]	X		

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMA: bone marrow aspirate; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; FU: follow-up; HBV: hepatitis B virus; HCO_3^-: bicarbonate; ICF: informed consent form; IRR: infusion-related reaction; LDH: lactate dehydrogenase; Moda: modakafusp alfa; MRD: measurable (minimal) residual disease; MRI: magnetic resonance imaging; NAb: neutralizing antibody; PCR: polymerase chain reaction; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); Q4W: every 4 weeks; Q12W: every 12 weeks; RBC: red blood cell; Rh factor: Rhesus factor; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; WBC: white blood cell.

Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

Footnotes for Schedule of Events (SOE) Tables 1 and 2 appear after SOE Table 2.

Footnotes for Appendix A Tables 1 and 2

a 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.

b Height will be measured only at the screening visit.

c All patients will have 1 standard local ECG collected and read locally at screening and at the end of dosing (+30 minutes) of all planned medications in the clinic on the days indicated.

d Vital signs will be measured at predose of each drug administration (eg, predose of daratumumab SC and predose of modakafusp alfa for modakafusp alfa in combination with daratumumab SC treatment), and after completing the administration of the last treatment medication (eg, after the completion of modakafusp alfa administration when daratumumab SC and modakafusp alfa are administered sequentially) on the days indicated. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. Vital signs will be measured at any time a patient complains of symptoms consistent with IRR or clinically indicated.

e Clinical imaging assessments to summarize status of known lesions should be based on available imaging at each respective time point.

f In case of an IRR, collect serum sample for circulating biomarkers, blood sample for flow cytometry, blood sample for RNA, and serum sample for immunogenicity (ADA), if clinical management of patient allows. Any decrease in infusion duration of modakafusp alfa must be discussed with and agreed on by the sponsor. If a patient presents with an IRR at any dose level, the duration of the infusion for 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 modakafusp alfa Pharmacy Manual for additional guidance.

g Imaging to assess bone disease is required for all patients at screening. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. Low-dose whole-body CT is recommended over conventional skeletal survey for the evaluation of multiple myeloma bone disease. Conventional skeletal survey can be used for the diagnosis of multiple myeloma 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 progressive disease). The same modality for assessment should be used throughout the study.

h Imaging to assess extramedullary disease is required for all patients at screening by PET-CT, MRI, or CT. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does 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 (±1 week) until a plateau or complete response 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 progressive disease.

i Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO_3^- or CO_2, blood urea nitrogen, calcium, chloride, magnesium, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein and may be collected up to 3 days before dosing. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 3 days old.

j Hematology will consist of hemoglobin, hematocrit, platelet count, leukocytes with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute neutrophil count (ANC) and may be collected up to 3 days before dosing. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 3 days old.

k Urinalysis (dipstick) includes bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic analysis only if clinically indicated: bacteria, RBCs, WBCs, casts, and crystals.

l Pregnancy test (refer to Section 9.5.6).
- Screening: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug. A negative urine or serum pregnancy test result will be required at screening and a negative urine or serum pregnancy test is required at within 72 hours of dosing at baseline.
- 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.
- A urine or serum pregnancy test is required at EOT in participants of childbearing potential.

m To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

n Sample to be collected at any time on Day 2 of the cycle.

o Urine M-protein 24-hour urine sample required while on treatment and during follow-up. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

p Serum FLC to be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

q Immunofixation in serum and urine is required for patients evaluated for CR; see Section 9.5.13.6. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

r A blood sample for quantification of immunoglobulins (IgM, IgG, and IgA) will be obtained. 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 immunoglobulins (in addition to quantitative IgM, IgG, and IgA) (see Section 9.5.13.3). To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

s For local analysis of disease assessment at screening, a standard BMA drawn before consent is acceptable provided this is collected within 5 weeks of the first dose.

t Blood samples for PK will be collected at time points specified in Appendix B.

u All patients should have a fresh BMA sample from screening sent for central cytogenetic analysis.

v At predose (before the administration of the first agent when drug combinations are administered), unless otherwise specified.

w Thyroid function tests (TSH, T3, T4) will be performed during screening, Cycle 3, and every 3 cycles (up to 3 days before dosing) thereafter until EOT and will be analyzed locally.

x Blood samples for immunogenicity (ADA/NAb) testing will be collected at predose on indicated visits during the treatment period and, if possible, at the EOT and PFS FU visits. In case of an infusion reaction, blood draws should be performed for central evaluation of immunogenicity (see Section 9.5.16). On days when dosing is not required, samples may be collected at any point during the clinic visit.

y Only repeat tests in parentheses for patients terminating treatment due to progressive disease if they were not performed before for progressive disease determination at the last visit, and for patients in CR if not performed before for CR confirmation.

z End-of-treatment laboratory assessments are to be performed before the patient starting a new treatment or a maximum of 30 days (+10 days) after the last dose.

aa Patients who discontinue study drug treatment for reasons other than progressive disease will continue PFS follow-up every 4 weeks from the EOT visit until the occurrence of progressive disease, death, the start of subsequent systemic antineoplastic therapy, study termination, whichever occurs first.

bb OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

cc At predose (before the administration of the first agent when drug combinations are administered) and also at 4 hours (±60 minutes) after the end of infusion of modakafusp alfa.

dd Immediately after the bone marrow aspirate/biopsy obtained for local disease assessment at screening and for confirmation of a suspected CR, an additional 1 mL of BMA will be collected for evaluation of MRD and sent to a central laboratory for analysis. If a BMA/biopsy drawn before consent, within 5 weeks of first dose, is used for local

disease assessment at screening, the first BMA pull at screening will be drawn for the MRD sample. Additionally, BMAs will be requested for MRD assessment at the time of suspected CR, and at 6, 12, and 24 months following CR confirmation. 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.

ee Following the collection of BMA for MRD sample at screening, an additional 3 mL pull of BMA will be collected for cytogenetic analysis and central evaluation of both tumor and immune fractions of bone marrow. Where country guidelines and/or regulations prohibit genomic analysis, a fluorescent in-situ hybridization will be used to evaluate cytogenetic abnormalities.

ff Sample collection allowance per country regulations.

gg It is required that, in addition to blood type (ABO) and Rh typing, the indirect antiglobulin test (also known as Indirect Coombs Test) be performed and the subject carries an identification wallet card with these results at all times during the study.

hh A portion of this sample may be used [redacted].

ii See Section 9.5.13.7 for details regarding interference testing for patients who received an IgG mAb as recent prior therapy.

[redacted]

kk Only for patients with test positive for HBV serologies (antibodies to hepatitis B core antigen and/or antibodies to hepatitis B surface antigen) or have a known history of HBV infection. Participants with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody 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.

Table 3 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 2a Dose Finding

Study Period/Cycle	Screening	Cycle 1 (28 d/cycle)				Cycle 2 (28 d/cycle)			
Day		**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**
Informed consent a	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Prior medication and treatment history	X								
Height and weight b	X	X				X			
ECOG performance status	X	X				X			
12-lead ECG c	X	X				X			
Physical examination (may be symptom-directed after screening visit)	X	X	X	X	X	X	X	X	X
Vital signs d	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 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 start of subsequent anticancer therapy, whichever occurs first (see Section 10.3)								
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (see Section 10.3)								
Dosing									
Modakafusp alfa infusion f		X				X			
Daratumumab SC		X	X	X	X	X	X	X	X
Safety Laboratory Assessments									
Chemistry i (local)	X	(X)	X	X	X	X	X	X	X
Hematology (local) j	X	(X)	X	X	X	X	X	X	X
Thyroid function tests (local) v	X								
Urinalysis (local) k	X								
Pregnancy test *(local)* l	X	X				X			
Serum β_2 microglobulin (*local*)	X								
Hepatitis B serology *(local)*	X								
HBV DNA *(local)* jj	X								

Table 3 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 2a Dose Finding

Study Period/Cycle	Screening	Cycle 1 (28 d/cycle)				Cycle 2 (28 d/cycle)			
Day		**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**
Window Allowed	**≤21 d**	**0**	**±2 d**	**±2 d**	**±2 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**
Blood type, Rh factor and indirect Coombs test *(local)* [ff]	X								
Disease Assessments									
Serum M-protein [m] *(local)*	X	(X) [m]				X			
24-hour urine M-protein *(local)* [n]	X	(X) [n]				X			
Serum FLC assay *(local)* [o]	X	(X) [o]				X			
Immunofixation: serum and urine *(local)* [p]	X	(X) [p]				X			
Serum sample for interference testing *(central)* [hh]						(X)			
Quantification of immunoglobulins *(local)* [q]	X	(X) [q]				X			
BMA for disease assessment *(local)* [r]	X	Sample to be collected at suspected CR to confirm response (CR/sCR)							
BMA for cytogenetics *(central)* [dd, gg]	X [t]								
BMA for MRD *(central)* [cc]	X	Sample to be collected at suspected CR and additional time points per description in footnote [cc]							
Investigator assessment of disease response/status						X			
Imaging Assessments									
Bone imaging [g]	X	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or progressive disease)							
Extramedullary disease imaging [h]	X	Additional assessments for extramedullary disease per the imaging schedule (Section 9.5.13.1)							
Clinical assessment of imaging response/status [e, g, h]		Additional assessments to be done per the imaging schedule Sections 9.5.13.1 and 9.5.13.2							
Biologic Laboratory Assessments *(central analysis)*									
Serum sample for PK [s]		Refer to PK collection Appendix B, Table 3							
Serum sample for immunogenicity (ADA/NAb) (only for Moda + Dara arm) [w, gg]		X		X		X		X	
Blood sample for flow cytometry [u]		X [bb]	X	X	X	X [bb]	X	X	X
Serum sample for circulating biomarkers [u]		X [bb]	X	X	X	X [bb]	X	X	X
Blood sample for RNA [u, ee]		X [bb]	X	X	X	X [bb]	X		

Table 3 Schedule of Events: Screening, Baseline, Cycle 1, and Cycle 2 for Modakafusp Alfa in Combination With Daratumumab SC in the Phase 2a Dose Finding

Study Period/Cycle	Screening	Cycle 1 (28 d/cycle)				Cycle 2 (28 d/cycle)			
Day		D1	D8	D15	D22	D1	D8	D15	D22
Window Allowed	≤21 d	0	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	±3 d
[redacted]									

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMA: bone marrow aspirate; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D: day; Dara: daratumumab SC; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; HBV: hepatitis B virus; HCO_3^-: bicarbonate; ICF: informed consent form; LDH: lactate dehydrogenase; Moda: modakafusp alfa; MRD: minimal residual disease; MRI: magnetic resonance imaging; NAb: neutralizing antibody; OS: overall survival; PCR: polymerase chain reaction; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); RBC: red blood cell; Rh factor: Rhesus factor; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; WBC: white blood cell.

Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

Footnotes for Schedule of Events (SOE) Tables 3-4 appear after SOE Table 4.

Table 4 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC the Phase 2a Dose Finding

Study Period/Cycle	Cycle 3 (28 d/cycle)		Cycle 4 (28 d/cycle)		Cycle 5 (28 d/cycle)		Cycle 6 (28 d/cycle)		Cycle 7 and beyond (28 d/cycle)	Cycle 11 (28 d/cycle)	EOT 30 (+10) days after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [y]	FU	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**		**PFS** Q4W (±1 wk) [z]	**OS** Q12W (± wk) [aa]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**			
Weight	X		X		X		X		X	X			
ECOG performance status	X		X		X		X		X	X	X		
12-lead ECG [c]	X		X		X		X		X	X	X		
Physical examination (may be symptom-directed)	X	X	X	X	X	X	X	X	X	X	X		
Vital signs [d]	X	X	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 (see Section 10.3)												
	SAEs will be reported from signing of ICF through 30 days after last dose of study drug, even if the patient starts nonprotocol therapy (see Section 10.3)												
Dosing													
Modakafusp alfa infusion [f]	X		X		X		X		X	X			
Daratumumab SC	X	X	X	X	X	X	X	X	X	X			
Safety Laboratory Assessments													
Chemistry *(local)* [i]	X		X		X		X		X	X	X		
Hematology *(local)* [j]	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test *(local)* [l]	X		X		X		X		X	X	X		
Thyroid function tests *(local)* [v]	X						X		X [v]		X		
HBV-DNA*(local)* [jj]	Every 12 weeks (±1 week) from Cycle 1 Day 1 until 6 months after the last dose of daratumumab SC												

Table 4 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC the Phase 2a Dose Finding

Study Period/Cycle	Cycle 3 (28 d/cycle)		Cycle 4 (28 d/cycle)		Cycle 5 (28 d/cycle)		Cycle 6 (28 d/cycle)		Cycle 7 and beyond (28 d/cycle)	Cycle 11 (28 d/cycle)	EOT 30 (+10) days after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [y]	FU	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**		**PFS** Q4W (±1 wk) [z]	**OS** Q12W (± wk) [aa]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**			
Disease Assessments													
Serum M-protein (*local*) [m]	X		X		X		X		X	X	(X) [x]	X	
24-hour urine M-protein (*local*) [n]	X		X		X		X		X	X	(X) [x]	X	
Serum FLC assay (*local*) [o]	X		X		X		X		X	X	(X) [x]	X	
Immunofixation: serum and urine (*local*) [p]	X		X		X		X		X	X	(X) [x]	X	
Serum sample for interference testing (*central*) [hh]	(X)		(X)		(X)		(X)		(X)	(X)	(X) [x]	(X)	
Quantification of immunoglobulins *(local)* [q]	X		X		X		X		X	X	(X) [x]	X	
BMA for disease assessment *(local)*	Sample to be collected at suspected CR to confirm response (CR/sCR); optional at the time of progression												
BMA for MRD *(central)* [cc]	Sample to be collected at suspected CR and additional time points per description in footnote [cc]												
[redacted]													
Investigator assessment of disease/response status	X		X		X		X		X		X	X	
Imaging Assessments													
Bone imaging [g]	Additional assessments for bone disease to be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or progressive disease)												
Extramedullary disease imaging [h]	Additional assessments for extramedullary disease per the imaging schedule (Section 9.5.13.1)												
Clinical assessment of imaging response/status [e, g, h]	Additional assessments to be done per the imaging schedule Sections 9.5.13.1 and 9.5.13.2												

Table 4 Schedule of Events: Cycle 3 Through EOT and FU for Modakafusp Alfa in Combination With Daratumumab SC the Phase 2a Dose Finding

Study Period/Cycle	Cycle 3 (28 d/cycle)		Cycle 4 (28 d/cycle)		Cycle 5 (28 d/cycle)		Cycle 6 (28 d/cycle)		Cycle 7 and beyond (28 d/cycle)	Cycle 11 (28 d/cycle)	EOT 30 (+10) days after last dose or start of subsequent systemic anticancer therapy, whichever occurs first [y]	FU	
Day	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**		**PFS** Q4W (±1 wk) [z]	**OS** Q12W (± wk) [aa]
Window Allowed	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**			
Biologic Laboratory Assessments (central analysis)													
Serum sample for PK [s]	Refer to PK collection Appendix B, Table 4												
Serum sample for immunogenicity (ADA/NAb) (only for Moda + Dara arm) [w, gg]	X		X		X		X		X	X	X	X	
Blood sample for flow cytometry [u]					X [bb]					X [bb]	X		
Serum sample for circulating biomarkers [u]					X [bb]					X [bb]	X		
Blood sample for RNA [u, ee]					X [bb]					X [bb]	X		

ADA: antidrug antibody; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMA: bone marrow aspirate; C: cycle; CO_2: carbon dioxide; CR: complete response; CT: computed tomography; D: day; Dara: daratumumab SC; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLC: free light chain; FU: follow-up; HBV: hepatitis B virus; HCO_3^-: bicarbonate; ICF: informed consent form; LDH: lactate dehydrogenase; Moda: modakafusp alfa; MRD: measurable (minimal) residual disease; MRI: magnetic resonance imaging; NAb: neutralizing antibody; OS: overall survival; PET-CT: positron emission tomography-computed tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PCR: polymerase chain reaction; Q4W: every 4 weeks; Q12W: every 12 weeks; RBC: red blood cell; Rh factor: Rhesus factor; SAE: serious adverse event; SC: subcutaneous; sCR: stringent complete response; WBC: white blood cell.

Crosses in parentheses "(X)" indicate tests are to be performed only under certain circumstances as indicated in associated footnote(s).

Footnotes for Schedule of Events (SOE) Tables 3-4 appear after SOE Table 4.

Footnotes for SOE Appendix Tables 3–4

a 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.

b Height will be measured only at the screening visit.

c All patients will have 1 standard local ECG collected and read locally at screening and at the end of dosing (+30 minutes) of all planned medications in the clinic on the days indicated.

d Vital signs will be measured at predose of each drug administration (eg, predose of daratumumab SC and predose of modakafusp alfa for modakafusp alfa in combination with daratumumab SC treatment), and after completing the administration of the last treatment medication (eg, after the completion of modakafusp alfa administration when daratumumab SC and modakafusp alfa are administered sequentially) on the days indicated. Vital signs include temperature, pulse, respiratory rate, oxygen saturation, and blood pressure. Vital signs will be measured at any time a patient complains of symptoms consistent with IRR or clinically indicated.

e Clinical imaging assessments to summarize status of known lesions should be based on available imaging at each respective time point.

f In case of an IRR, collect serum sample for circulating biomarkers, blood sample for flow cytometry, blood sample for RNA, and serum sample for immunogenicity (ADA), if clinical management of patient allows. Any decrease in infusion duration of modakafusp alfa must be discussed with and agreed on by the sponsor. If a patient presents with an IRR at any dose level, the duration of the infusion for 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 modakafusp alfa Pharmacy Manual for additional guidance.

g Imaging to assess bone disease is required for all patients at screening. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does not need to be repeated as part of screening. Low-dose whole-body CT is recommended over conventional skeletal survey for the evaluation of multiple myeloma bone disease. Conventional skeletal survey can be used for the diagnosis of multiple myeloma 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 progressive disease). The same modality for assessment should be used throughout the study.

h Imaging to assess extramedullary disease is required for all patients at screening by PET-CT, MRI, or CT. Imaging performed within 5 weeks of the planned first dose of study drug can be used as baseline evaluations and does 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 (±1 week) until a plateau or complete response 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 progressive disease.

i Chemistry will consist of albumin, ALT, alkaline phosphatase, AST, HCO_3^- or CO_2, blood urea nitrogen, calcium, chloride, magnesium, potassium, sodium, phosphate, creatinine, total bilirubin, LDH, urate, blood glucose (nonfasting), and standard C-reactive protein and may be collected up to 3 days before dosing. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 3 days old.

j Hematology will consist of hemoglobin, hematocrit, platelet count, leukocytes with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils) and absolute neutrophil count (ANC) and may be collected up to 3 days before dosing. It is not necessary to repeat these tests on C1D1 predose if the tests performed at screening are less than 3 days old.

k Urinalysis (dipstick) includes bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, pH, protein, specific gravity, turbidity and color, and urobilinogen. Microscopic analysis only if clinically indicated: bacteria, RBCs, WBCs, casts, and crystals.

l Pregnancy test (refer to Section 9.5.6).

- Screening: Participants of childbearing potential must have 2 negative pregnancy tests before starting study drug. A negative urine or serum pregnancy test result is required at screening, and a negative urine or serum pregnancy test result is required at baseline.
- 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.
- A urine or serum pregnancy test is required at EOT in participants of childbearing potential.

m To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

n Urine M-protein 24-hour urine sample required while on treatment and during follow-up. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

o Serum FLC to be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

p Immunofixation in serum and urine is required for patients evaluated for CR; see Section 9.5.13.6. To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

q A blood sample for quantification of immunoglobulins (IgM, IgG, and IgA) will be obtained. 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 immunoglobulins (in addition to quantitative IgM, IgG, and IgA) (see Section 9.5.13.3). To be repeated at baseline (C1D1) if screening sample was taken more than 7 days before C1D1.

r For local analysis of disease assessment, a standard BMA drawn before consent is acceptable provided this is collected within 5 weeks of the first dose.

s Blood samples for PK will be collected at time points specified in Appendix B.

t All patients should have a fresh BMA sample from screening sent for central cytogenetic analysis.

u At predose (before the administration of the first agent when drug combinations are administered), unless otherwise specified.

v Thyroid function tests (TSH, T3, T4) will be performed during screening, Cycle 3, and every 3 cycles (up to 3 days before dosing) thereafter until EOT and will be analyzed locally.

w Blood samples for immunogenicity (ADA/NAb) testing will be collected at predose on indicated visits during the treatment period and, if possible, at the EOT and PFS FU visits. In case of an infusion reaction, blood draws should be performed for central evaluation of immunogenicity (see Section 9.5.16). On days when dosing is not required, samples may be collected at any point during the clinic visit.

x Only repeat tests in parentheses for patients terminating treatment due to progressive disease if they were not performed before for progressive disease determination at the last visit, and for patients in CR if not performed before for CR confirmation.

y End-of-treatment laboratory assessments are to be performed before the patient starting a new treatment or a maximum of 30 days (+10 day) following the last dose.

z Patients who discontinue study drug treatment for reasons other than progressive disease will continue PFS follow-up every 4 weeks from the EOT visit until the occurrence of progressive disease, death, the start of subsequent systemic antineoplastic therapy, study termination, whichever occurs first.

aa OS follow-up continues every 12 weeks until death, study termination, or patient withdrawal.

bb At predose (before the administration of the first agent when drug combinations are administered), and also at 4 hours (±60 minutes) after the end of infusion of modakafusp alfa.

cc Immediately after the bone marrow aspirate/biopsy obtained for local disease assessment at screening and for confirmation of a suspected CR, an additional 1 mL of BMA will be collected for evaluation of MRD and sent to a central laboratory for analysis. If a BMA/biopsy drawn before consent, within 5 weeks of first dose, is used for local disease assessment at screening, the first BMA pull at screening will be drawn for the MRD sample. Additionally, BMAs will be requested for MRD assessment at the time of suspected CR, and at 6, 12, and 24 months following CR confirmation. 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.

dd Following the collection of BMA for MRD sample at screening, an additional 3 mL pull of BMA will be collected for cytogenetic analysis and central evaluation of both tumor and immune fractions of bone marrow. Where country guidelines and/or regulations prohibit genomic analysis, a fluorescent in-situ hybridization will be used to evaluate cytogenetic abnormalities.

ee Sample collection allowance per country regulations.

ff It is required that, in addition to blood type (ABO) and Rh blood typing, the indirect antiglobulin test (also known as Indirect Coombs Test) be performed and that the subject carries an identification wallet card with these results at all times during the study.

gg A portion of this sample may be used for [redacted].

hh See Section 9.5.13.7 for details regarding interference testing for patients who received an IgG mAb as recent prior therapy.

[redacted]

jj Only for patients with test positive for HBV serologies (antibodies to hepatitis B core antigen and/or antibodies to hepatitis B surface antigen) or have a known history of HBV infection. Participants with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody 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.

Appendix B PK Sampling

Table 1 PK Sampling Cycle 1 and Cycle 2 (Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation)

Time Point	Modakafusp Alfa PK (Cycle 1 and Cycle 2)					Daratumumab PK (Cycle 1 and Cycle 2)				
	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22
Predose (within 30 min before start of modakafusp alfa infusion and/or daratumumab SC administration) [a]	X		X	X	X	X		X	X	X
End of infusion (±10 min)	X									
2-4 h after end of infusion (±30 min)	X									
During the clinic visit		X					X			

PK: pharmacokinetic(s); SC: subcutaneous.

[a] The timing of the morning visits should occur at approximately the same time as the morning dosing on previous dosing visits. Blood sample for Day 1 will be collected within 30 minutes before start of the administration of the first agent when drug combinations are administered. Blood samples for Days 8, 15, and 22 will be within 30 minutes before the administration of daratumumab SC.

Table 2 PK Sampling: Cycles 3 and Beyond (Modakafusp Alfa in Combination With Daratumumab SC in the Phase 1 Dose Escalation)

Time Point	Modakafusp PK (Cycle 3 and Beyond)			Daratumumab PK (Cycles 3, 5 and Beyond) [b]		
	Day 1	Day 2 [a]	EOT	Day 1	Day 2 [a]	EOT
Predose (within 30 min before start of daratumumab SC administration)				X		
End of infusion	X					
2-4 hours after end of infusion (±30 min)	X					
During the clinic visit		X	X		X	X

EOT: end of treatment; min: minute: PK: pharmacokinetic(s); SC: subcutaneous.

[a] Day 2 of Cycles 5 and 11 only

[b] Daratumumab PK will be collected every 2 cycles from Cycles 3 and 5 and beyond, and at the EOT.

Table 3 PK Sampling: Cycle 1 and Cycle 2 in the Phase 2a Dose Finding

	Modakafusp PK (Cycle 1 and Cycle 2)				Daratumumab PK (Cycle 1 and Cycle 2)			
Time Point	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**
Predose (within 30 min before start of infusion) [a]	X	X	X	X	X	X	X	X
End of infusion (±10 min)	X							
2-4 hours after end of infusion (±30 min)	X							

PK: pharmacokinetic(s); SC: subcutaneous.

[a] The timing of the morning visits should occur at approximately the same time as the morning dosing on previous dosing visits. Blood sample for Day 1 will be collected within 30 minutes before start of administration of the first agent when drug combinations are administered. Blood sample for Days 8, 15, and 22 will be collected within 30 minutes before the start the daratumumab SC administration.

Table 4 PK Sampling: Cycle 3 and Beyond in Phase 2a Dose Finding

	Modakafusp PK		Daratumumab PK	
Time Point	**(Cycle 3 and Beyond)**	**EOT**	**(Cycle 3, 5, and Beyond) [a]**	**EOT**
	Day 1		**Day 1**	
Predose (within 30 min before start of daratumumab SC administration)			X	
End of infusion	X			
2-4 hours after end of infusion (±30 min)	X			
During the clinical visit		X		X

EOT: end of treatment; PK: pharmacokinetic(s); SC subcutaneous.

[a] Daratumumab PK will be collected every 2 cycles from Cycles 3 and 5 and beyond, and at the EOT.

Appendix C Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients 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 patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each patient who participates in the study, and document the date of (e)consent in the patient's medical chart. Valid informed (e)consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

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

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E 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 (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‡.
   - 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).

PET-CT: [^{18}F]fluorodeoxyglucose PET with CT.
* 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).

Appendix E Table 1 IMWG Criteria for Response

Response Category	**Response Criteria** (Kumar et al. 2016; Rajkumar et al. 2011)
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).

Appendix E Table 1 IMWG Criteria for Response

Response Category	Response Criteria (Kumar et al. 2016; Rajkumar et al. 2011)
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	• Increase of 25% from lowest response value in one or more of the following: – Serum M-component (absolute increase must be ≥0.5 g/dL) – Urine M-component (absolute increase must be ≥200 mg per 24 hours) – 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%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

BM: bone marrow; CR: complete response; FLC: free light chain; MR: minimal response; ORR: objective response rate; PD: progression of disease; sCR: stringent complete response; SD: stable disease; SPD: maximal perpendicular diameter; 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.

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. A diagnosis of progression of disease must be confirmed by 2 consecutive assessments.

Plasmacytomas: A definite increase in the size is defined as a ≥50% increase from nadir as measured serially by the sum of the products of the maximal perpendicular diameter of the measurable lesion or a ≥50% increase in the longest diameter of a previous lesion with ≥1 cm short axis. 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 non-measurable. The requirement for bi-directional measurements applies only to plasmacytomas. For defining nadir, in the case where a value is felt to be a spurious result per physician/IRC discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Appendix F ECOG Scale for Performance Status

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

Source: (Oken et al. 1982).

Appendix G Protocol History

Date	Amendment Number	Amendment Type	Region
03 April 2024	Amendment 1 v2	Substantial	Global
28 February 2024	Amendment 1 v1 (not implemented)	Substantial	Global
15 September 2023	Initial Protocol US v1	Nonsubstantial; Regional	United States
23 June 2023	Initial Protocol GB v1	Nonsubstantial; Regional	United Kingdom
05 April 2023	Initial Protocol DE v2	Nonsubstantial; Regional	Germany
05 April 2023	Initial Protocol DE v1	Nonsubstantial; Regional	Germany
27 January 2023	Initial Protocol CZ v1	Nonsubstantial; Regional	Czech Republic
14 December 2022	Initial Protocol FR v1	Nonsubstantial; Regional	France
16 August 2022	Initial protocol	Not applicable	Global

Protocol Amendment 1 v2 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 1 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 1 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.	8.6.1.3 Criteria for Dose Interruption	Addition of Table 8.d with the dose modifications for modakafusp alfa bleeding TEAEs.	Updated to mitigate the risk of fatal hemorrhagic events.
2.	8.6.1.5 Criteria for Discontinuation	Modification of phase name to indicate “dose escalation” rather than “safety lead-in”. Removal of criteria related to Grade 4 life threatening TEAEs.	Updated to align with changes made in this protocol amendment.
3.	8.8 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.

Protocol Amendment 1 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**	
4.	8.10.1.2 Low Platelet Count	Addition of mention to reference Table 8.d with the dose modifications for modakafusp alfa bleeding TEAEs	Updated to mitigate the risk of fatal hemorrhagic events.

Protocol Amendment 1 v1 Summary and Rationale (Not Implemented)

As of 25 October 2023, Takeda decided to not proceed to the Phase 2a part after completing phase 1 dose escalation of Study TAK-573-2001. As of 20 November 2023, Takeda decided to discontinue the development of modakafusp alfa, including Study TAK-573-2001. These decisions were made due to strategic reasons and not due to any safety concerns with modakafusp alfa.

The purpose of this amendment (Amendment 1 v1; not implemented) is to ease the burden of protocol-mandated assessments on remaining patients in phase 1, and to confirm the cancellation of phase 2a.

Any country specific protocol was to be followed before the implementation of this global Protocol Amendment 1 v1 (not implemented).

Phase 1 Dose Escalation:

The primary reason for Amendment 1 v1 (not implemented) in this phase is to reduce the data collection activities and study assessments for remaining patients in this study. Upon implementation of this amendment, data collection activities will be limited to dosing of study drug and the following safety assessments: all serious adverse events (SAEs), 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.

Phase 2a Dose Finding:

The primary reason for Amendment 1 v1 (not implemented) in this phase is to confirm that the phase 2a dose finding part of the study was terminated on 25 October 2023.

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 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***
Changes for Phase 1 Dose Escalation:			
1.	• Section 2.0 STUDY SUMMARY • Section 6.1 Overview of Study Design • Section 6.3.1 Duration of an Individual Patient's Study Participation • Section 9.0 STUDY CONDUCT • Section 9.5 Study Procedures • Section 9.5.6 Pregnancy Test • Section 9.5.8 ECOG Performance Status • Section 9.5.9 AEs • Section 9.5.11 ECG • Section 9.5.12 Clinical Laboratory Evaluations • Section 10.2 Procedures for Recording and Reporting AEs and SAEs • Section 10.3 Monitoring of AEs and Period of Observation • Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events • Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose) • Section 10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities • Section 13.0 STATISTICAL METHODS	Revise protocol throughout to identify that the majority of study assessments will be discontinued to ease the burden of protocol-mandated assessments on patients, including simplifying the SOE to apply to the remainder of the study (Appendix A Table 1) Define the ongoing safety assessments of Amendment 1 as follows: • All data collection activities will be limited to: - Dosing (drug exposure) – 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 – Medication errors (including overdose). • All other study assessments are no longer required	To clarify that no further formal efficacy or safety analyses are planned and select safety assessments are retained to ensure patient safety

Protocol Amendment 1 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**	
	• Section 13.1 Statistical and Analytical Plans • Section 13.1.1 Analysis Sets • Section 13.1.8 Safety Analysis • Appendix A Schedules of Events (Appendix A Table 1)		
2.	• Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting • Section 9.5 Study Procedures • Section 9.11 Posttreatment Follow-up Assessments (PFS and OS)	Discontinue the PFS and OS follow-up periods	To clarify that patients no longer need to be followed once they come off study treatment, as no further efficacy or formal safety analyses will be performed in the study.
3.	• Section 9.5.13 Disease Assessment • Section 9.5.13.1 Extramedullary Disease Imaging • Section 9.5.13.2 Bone Imaging • Section 9.5.13.3 Quantification of Immunoglobulins • Section 9.5.13.4 Quantification of M-Protein in Serum and Urine • Section 9.5.13.5 Serum FLC Assay • Section 9.5.13.6 Immunofixation of Serum and Urine • Section 9.5.13.7 Interference Assay • Section 9.5.13.8 Bone Marrow Aspirate • Section 9.5.13.9.1 Disease Assessment • Section 9.5.13.9.2 Cytogenetics	Discontinue all disease and efficacy response assessments, including central laboratory assessments of efficacy and safety, for protocol purposes	To clarify that no further efficacy or formal safety analyses will be performed for the study.

Protocol Amendment 1 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**	
	• Section 9.5.13.10 Central Laboratory Evaluations • Section 13.1.3 Efficacy Analysis • Section 13.1.3.1 Analysis of Primary Efficacy Endpoint • Section 13.1.3.2 Analysis of Secondary Efficacy Endpoints • Section 13.1.3.2.2 Phase 2a Dose Finding		
4.	• Section 9.5.14 Biomarker, PD, and PK Samples • Section 9.5.14.1 Primary Specimen Collection • Section 9.5.14.2 PK Sampling • Section 9.5.14.3.1 [redacted] • Section 9.5.14.3.2 [redacted] • Section 9.5.15 [redacted] • Section 9.5.16 Immunogenicity Sample Collection • Section 13.1.4 PK Analysis • Section 13.1.5 [redacted] • Section 13.1.6 PK/PD Analysis • Section 13.1.7 Immunogenicity Analyses	Discontinue biomarker, pharmacodynamic (PD), pharmacokinetic (PK), and immunogenicity sampling, and pharmacogenomic measurements for ongoing patients	No further analyses will be performed
5.	• Section 6.2 Number of Patients	Confirm number of patients enrolled as of Amendment 1 and that no additional patients will be enrolled in the study	To clarify that no additional patients will be enrolled in the study.
6.	• Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting	Confirm prompt notification by sponsor to investigators, institutions, and regulatory authorities should a clinical study prematurely discontinue	To clarify notification process by sponsor should a clinical study be prematurely terminated or suspended

Protocol Amendment 1 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**	
7.	• Section 6.5 Posttrial Access	Add text that after data cutoff, ongoing patients must transition to the posttrial (PTA) program once it becomes available in their country	To clarify PTA program
8.	• Section 6.5.1 Duration of PTA	Revise conditions under which sponsor could terminate PTA of modakafusp alfa	To make consistent with TAK 573-1501 Protocol Amendment 1
9.	• Section 9.5.7 Concomitant Medications and Procedures	Discontinue collection of concomitant medications and procedures	To confirm that no further analyses will be performed
10.	• Section 9.5.12 Clinical Laboratory Evaluations • Section 9.5.12.1 Clinical Chemistry, Hematology, Urinalysis and Indirect Antiglobulin Test (Coombs Test)	Confirm that only local laboratory evaluations should be entered into the eCRF only if required to understand a TEAE	To clarify what laboratory evaluations should continue to entered into the eCRF
Changes for Phase 2a Dose Finding:			
1.	• Section 2.0 STUDY SUMMARY • Section 4.4 Modakafusp Alfa Dose Selection for Phase 2a Dose Finding in Combination With Daratumumab SC • Section 5.1.1 Primary Objectives • Section 5.1.2 Secondary Objectives • Section 5.1.3 Exploratory Objectives • Section 5.2.1 Primary Endpoints • Section 5.2.2 Secondary Endpoints • Section 5.2.3 Exploratory Endpoints • Section 6.1 Overview of Study Design • Figure 6.a Schematic of TAK-573-2001 Study Design • Section 6.2.2 Phase 2a Dose Finding	Confirm that the Phase 2a Dose Finding part of the study was terminated on 25 October 2023; therefore, all planned study activities during this phase are now cancelled	Sponsor decision to cancel this part of the study

Protocol Amendment 1 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**	
	• Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures • Section 6.3.4 Total Study Duration • Section 6.4 Randomization in Phase 2a Dose Finding • Section 9.4 Treatment Group Assignments • Section 9.5 Study Procedures • Section 13.2 Determination of Sample Size • Appendix A Schedules of Events (Appendix A Table 1)		

INITIAL PROTOCOL US V1 SUMMARY OF CHANGES

Initial Protocol US v1 Summary Rationale:

This section describes the changes to the Initial Protocol Incorporating US v1. The primary reasons for this amendment are to:

- Change the current eligibility criteria for phase 2a to not only require refractoriness to lenalidomide, but also prior exposure to a proteasome inhibitor (PI).
- Modify the dose limiting toxicity (DLT) criteria for neutropenia, infusion-related reactions (IRRs), and rash.
- Modify the DLT criteria for Grade 4 thrombocytopenia lasting more than 14 consecutive days to lasting more than 7 consecutive days.
- Modify dose modification recommendations for modakafusp alfa nonhematological toxicities (Table 8.b) to indicate that modakafusp alfa should be resumed at a reduced dose after recovery to Grade ≤1 or baseline in the event of symptomatic Grade ≥3 non-hematological toxicities; but for asymptomatic Grade 3 and Grade 4 nonhematological laboratory AEs, modakafusp alfa can be resumed either at the same dose or a reduced dose at the discretion of the investigator for the first occurrence and then reduce modakafusp alfa by 1 dose level for subsequent occurrence.

- Clarify that patients who experience Grade 4 life-threatening TEAEs will be permanently withdrawn from the study.

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.

Initial Protocol US v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 4.2.2 Study Population Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Inclusion Criterion #5a was updated to include prior treatment with proteasome inhibitor and lenalidomide.	Response to United States health authority request.
Section 8.3.1 Definitions of DLT	Modify the DLT criteria for neutropenia, IRRs, and rash. Modify the DLT criteria for Grade 4 thrombocytopenia lasting more than 14 consecutive days to lasting more than 7 consecutive days.	Response to United States health authority request.
Section 8.6.1.3 Criteria for Dose Interruption	Modify dose modification recommendations for modakafusp alfa nonhematological toxicities.	Response to United States health authority request.
Section 8.6.1.5 Criteria for Discontinuation	Clarify that patients who experience Grade 4 life-threatening TEAEs will be permanently withdrawn from the study.	Response to United States health authority request.

INITIAL PROTOCOL GB V1 SUMMARY OF CHANGES

Initial Protocol GB v1 Summary Rationale:

This section describes the changes to the Initial Protocol Incorporating GB v1. The primary reasons for this amendment are to:

- Clarify that patients with seropositive results for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV at screening be excluded, and added HCV and HIV serology tests besides HBV serology tests at screening.
- Update inclusion criterion for phase 2a on prior treatment to include proteasome inhibitor and lenalidomide.
- Clarify that investigators are part of the decision-making team for determining dose escalation stopping decisions, study stop or termination.
- Add definition of sterile to contraception language.

- Add that daratumumab will be discontinued if a patient is pregnant.
- Add that patients must not receive a live vaccine during treatment, 90 days after the last dose of daratumumab, and 1 week after the last dose of 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.

Initial Protocol GB v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.2 Exclusion Criteria Section 9.5.12.1 Clinical Chemistry, Hematology, Urinalysis and Indirect Antiglobulin Test (Coombs Test) Appendix A Schedules of Events	Exclusion Criterion #9 was clarified to exclude patients with seropositive results for hepatitis B virus, hepatitis C virus, and HIV testing at screening.	Response to United Kingdom health authority request.
Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Inclusion Criterion #5a was updated to include prior treatment with proteasome inhibitor and lenalidomide.	Response to United Kingdom health authority request.
[redacted]	[redacted]	Response to United Kingdom health authority request.
Section 7.1 Inclusion Criteria Section 8.9.1 Contraception and Pregnancy Avoidance Procedures	Added definition of sterile (via hysterectomy, salpingectomy or oophorectomy).	Response to United Kingdom health authority request.
Section 8.9.2 Pregnancy	Added that daratumumab will be discontinued if a patient is pregnant.	Response to United Kingdom health authority request.
Section 8.7 Prohibited Concomitant Medications and Procedures	Added that patients must not receive a live vaccine during treatment, 90 days after the last dose of daratumumab, and 1 week after the last dose of modakafusp alfa.	Response to United Kingdom health authority request.

INITIAL PROTOCOL DE V2 SUMMARY OF CHANGES

Initial Protocol DE v2 Summary and Rationale:

This section describes the changes to the Initial Protocol incorporating DE v2. The primary reasons for this amendment are to:

- Modify the inclusion criteria that patients in phase 1 must have received anti-BCMA (anti–B-cell maturation antigen) therapy and that patients in phase 2a must have been exposed to both a proteosome inhibitor (PI) and lenalidomide.

- Provide consistent antiviral prophylaxis guidance.

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.

Initial Protocol DE v2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 4.2.2 Study Population Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Modified the inclusion criteria that patients in phase 1 must have received anti-BCMA (anti–B-cell maturation antigen) therapy and that patients in phase 2a must have been exposed to both a proteosome inhibitor (PI) and lenalidomide.	To ensure patient access to the study per local guidance.
Section 8.1.1.5 Prophylaxis Against Risk of Infection Section 8.1.1.5 Prophylaxis Against Risk of Infection Section 8.10.1.3 Prophylaxis	Provided consistent antiviral prophylaxis guidance.	To provide consistent guidance.

INITIAL PROTOCOL DE V1 SUMMARY OF CHANGES

Initial Protocol DE v1 Summary and Rationale:

This section describes the changes to the Initial Protocol incorporating DE v1. The primary reason for this amendment is to ensure that the sponsor will keep the study sample data confidential and in a pseudonymized form.

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.

Initial Protocol DE v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 15.3 Patient Confidentiality	Ensure that the sponsor will keep the study sample data confidential and in a pseudonymized form.	Response to Germany Ethics Committee request.

INITIAL PROTOCOL CZ V1 SUMMARY OF CHANGES

Initial Protocol CZ v1 Summary Rationale:

This section describes the changes to the Initial Protocol incorporating CZ v1. The primary reason for this amendment is to prohibit live vaccines for 90 days after modakafusp alfa treatment.

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.

Initial Protocol CZ v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.1 Inclusion Criteria Section 8.7 Prohibited Concomitant Medications and Procedures	Inclusion Criterion #8 revised to exclude live vaccines within 30 days before first administration of study treatment for patients. Live vaccines are excluded during study treatment and for 90 days after the last dose of modakafusp alfa.	Response to Czech Republic health authority request.

INITIAL PROTOCOL FR V1 SUMMARY OF CHANGES

Initial Protocol FR v1 Summary and Rationale:

This section describes the changes to the Initial Protocol incorporating FR v1. The primary reasons for this amendment are to:

- Clarify in the inclusion criteria that patients in phase 2a must have been exposed to both a proteosome inhibitor and immunomodulatory drug.
- Revise the inclusion criteria to increase the duration of the washout period to 14 days for patients who have received radiation therapy for localized bone lesions.
- Add that hospitalization is required for the first infusion of modakafusp alfa in combination with daratumumab administered subcutaneously.

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.

Initial Protocol FR v1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 4.2.2 Study Population Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Clarified in the inclusion criteria that patients in phase 2a must have been exposed to both a proteasome inhibitor and an immunomodulatory drug.	To ensure patient access to the study per local guidance.
Section 7.1 Inclusion Criteria	Revised the inclusion criteria to increase the duration of the washout period to 14 days for patients who have received radiation therapy for localized bone lesions.	To ensure patient safety.
Section 8.1.1.2 Administration Section 8.1.1.4 Postinfusion Medication and Monitoring Appendix A Schedule of Events	Added that hospitalization is required for the first infusion of modakafusp alfa in combination with daratumumab administered subcutaneously.	To ensure patient safety.

Signature Page for TAK-573-2001 Protocol Amend 02 US v1 2024-09-19
Title: Amend 02 US v1 to A Phase 1/2a Open-label Study to Evaluate the Safety, T

Approval	[redacted] Clinical 25-Sep-2024 21:53:13 GMT+0000

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